

- 307) bombesin/gastrin releasing peptide receptors — a cathepsin type protease;
- 308) bombesin/gastrin releasing peptide receptors — bombesin/gastrin releasing peptide receptors;
- 5 309) bombesin/gastrin releasing peptide receptors — cathepsin B;
- 310) bombesin/gastrin releasing peptide receptors — cathepsin D;
- 311) bombesin/gastrin releasing peptide receptors — to cathepsin K;
- 312) bombesin/gastrin releasing peptide receptors — cathepsin L;
- 313) bombesin/gastrin releasing peptide receptors — cathepsin O;
- 10 314) bombesin/gastrin releasing peptide receptors — fibroblast activation protein;
- 315) bombesin/gastrin releasing peptide receptors — folate binding receptors;
- 316) bombesin/gastrin releasing peptide receptors —
- 15 gastrin/cholecystokinin type B receptor;
- 317) bombesin/gastrin releasing peptide receptors — glutamate carboxypeptidase II or (PSMA);
- 318) bombesin/gastrin releasing peptide receptors — guanidinobenzoate;
- 20 319) bombesin/gastrin releasing peptide receptors — laminin receptor;
- 320) bombesin/gastrin releasing peptide receptors — matrilysin;
- 321) bombesin/gastrin releasing peptide receptors — matrilysin;
- 322) bombesin/gastrin releasing peptide receptors — melanocyte stimulating hormone receptor;

- 323) bombesin/gastrin releasing peptide receptors — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 5 324) bombesin/gastrin releasing peptide receptors — norepinephrine transporters;
- 325) bombesin/gastrin releasing peptide receptors — nucleoside transporter proteins;
- 326) bombesin/gastrin releasing peptide receptors — peripheral benzodiazepam binding receptors;
- 10 327) bombesin/gastrin releasing peptide receptors — seprase;
- 328) bombesin/gastrin releasing peptide receptors — sigma receptors;
- 329) bombesin/gastrin releasing peptide receptors — somatostatin receptors;
- 330) bombesin/gastrin releasing peptide receptors — stromelysin 3;
- 15 331) bombesin/gastrin releasing peptide receptors — trypsin;
- 332) bombesin/gastrin releasing peptide receptors — MMP 1;
- 333) bombesin/gastrin releasing peptide receptors — MMP 2;
- 334) bombesin/gastrin releasing peptide receptors — MMP 3;
- 335) bombesin/gastrin releasing peptide receptors — MMP 7;
- 20 336) bombesin/gastrin releasing peptide receptors — MMP 9;
- 337) bombesin/gastrin releasing peptide receptors — membrane type matrix metalloproteinase 1;
- 338) bombesin/gastrin releasing peptide receptors — MMP 12;
- 339) bombesin/gastrin releasing peptide receptors — MMP 13;
- 25 340) bombesin/gastrin releasing peptide receptors — a tumor antigen;

- 341) fibroblast activation protein — a cathepsin type protease;
- 342) fibroblast activation protein — cathepsin D;
- 343) fibroblast activation protein — to cathepsin K;
- 344) fibroblast activation protein — cathepsin L;
- 5 345) fibroblast activation protein — cathepsin O;
- 346) fibroblast activation protein — fibroblast activation protein;
- 347) fibroblast activation protein — folate binding receptors;
- 348) fibroblast activation protein — gastrin/cholecystokinin type B
receptor;
- 10 349) fibroblast activation protein — glutamate carboxypeptidase II or
(PSMA);
- 350) fibroblast activation protein — guanidinobenzoatase;
- 351) fibroblast activation protein — laminin receptor;
- 352) fibroblast activation protein — matrilysin;
- 15 353) fibroblast activation protein — matripase;
- 354) fibroblast activation protein — melanocyte stimulating hormone
receptor;
- 355) fibroblast activation protein — nitrobenzylthioinosine-binding
receptors or (nucleoside transporter);
- 20 356) fibroblast activation protein — norepinephrine transporters;
- 357) fibroblast activation protein — nucleoside transporter proteins;
- 358) fibroblast activation protein — peripheral benzodiazepam binding
receptors;
- 359) fibroblast activation protein — plasmin;
- 25 360) fibroblast activation protein — seprase;

- 361) fibroblast activation protein — sigma receptors;
- 362) fibroblast activation protein — somatostatin receptors;
- 363) fibroblast activation protein — stromelysin 3;
- 364) fibroblast activation protein — trypsin;
- 5 365) fibroblast activation protein — MMP 1;
- 366) fibroblast activation protein — MMP 2;
- 367) fibroblast activation protein — MMP 3;
- 368) fibroblast activation protein — MMP 7;
- 369) fibroblast activation protein — MMP 9;
- 10 370) fibroblast activation protein — membrane type matrix metalloproteinase I;
- 371) fibroblast activation protein — MMP 12;
- 372) fibroblast activation protein — MMP 13;
- 373) fibroblast activation protein — a tumor antigen;
- 15 374) glutamate carboxypeptidase II or PSMA — cathepsin D;
- 375) glutamate carboxypeptidase II or PSMA — to cathepsin K;
- 376) glutamate carboxypeptidase II or PSMA — cathepsin L;
- 377) glutamate carboxypeptidase II or PSMA — cathepsin O;
- 378) glutamate carboxypeptidase II or PSMA — fibroblast activation
20 protein;
- 379) glutamate carboxypeptidase II or PSMA — folate binding
receptors;
- 380) glutamate carboxypeptidase II or PSMA — gastrin/cholecystokinin
type B receptor;

- 381) glutamate carboxypeptidase II or PSMA — glutamate
carboxypeptidase II or (PSMA);
- 382) glutamate carboxypeptidase II or PSMA — guanidinobenzoatase;
- 383) glutamate carboxypeptidase II or PSMA — laminin receptor;
- 5 384) glutamate carboxypeptidase II or PSMA — matrilysin;
- 385) glutamate carboxypeptidase II or PSMA — matripase;
- 386) glutamate carboxypeptidase II or PSMA — melanocyte stimulating
hormone receptor;
- 387) glutamate carboxypeptidase II or PSMA — nitrobenzylthioinosine-
10 binding receptors or (nucleoside transporter);
- 388) glutamate carboxypeptidase II or PSMA — nucleoside transporter
proteins;
- 389) glutamate carboxypeptidase II or PSMA — peripheral
benzodiazepam binding receptors;
- 15 390) glutamate carboxypeptidase II or PSMA — seprase;
- 391) glutamate carboxypeptidase II or PSMA — sigma receptors;
- 392) glutamate carboxypeptidase II or PSMA — somatostatin receptors;
- 393) glutamate carboxypeptidase II or PSMA — stromelysin 3;
- 394) glutamate carboxypeptidase II or PSMA — trypsin;
- 20 395) glutamate carboxypeptidase II or PSMA — MMP 1;
- 396) glutamate carboxypeptidase II or PSMA — MMP 2;
- 397) glutamate carboxypeptidase II or PSMA — MMP 3;
- 398) glutamate carboxypeptidase II or PSMA — MMP 7;
- 399) glutamate carboxypeptidase II or PSMA — MMP 9;

- 400) glutamate carboxypeptidase II or PSMA — membrane type matrix metalloproteinase I;
- 401) glutamate carboxypeptidase II or PSMA — MMP 12;
- 402) glutamate carboxypeptidase II or PSMA — MMP 13;
- 5 403) glutamate carboxypeptidase II or PSMA — a tumor antigen;
- 404) laminin receptor — a cathepsin type protease;
- 405) laminin receptor — cathepsin B;
- 406) laminin receptor — cathepsin D;
- 407) laminin receptor — to cathepsin K;
- 10 408) laminin receptor — cathepsin L;
- 409) laminin receptor — cathepsin O;
- 410) laminin receptor — fibroblast activation protein;
- 411) laminin receptor — folate binding receptors;
- 412) laminin receptor — gastrin/cholecystokinin type B receptor;
- 15 413) laminin receptor — guanidinobenzoatase;
- 414) laminin receptor — laminin receptor;
- 415) laminin receptor — matrilysin;
- 416) laminin receptor — matripase;
- 417) laminin receptor — melanocyte stimulating hormone receptor;
- 20 418) laminin receptor — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 419) laminin receptor — norepinephrine transporters;
- 420) laminin receptor — nucleoside transporter proteins;
- 421) laminin receptor — peripheral benzodiazepam binding receptors;
- 25 422) laminin receptor — seprase;

- 423) laminin receptor — sigma receptors;
- 424) laminin receptor — somatostatin receptors;
- 425) laminin receptor — stromelysin 3;
- 426) laminin receptor — trypsin;
- 5 427) laminin receptor — MMP 1;
- 428) laminin receptor — MMP 2;
- 429) laminin receptor — MMP 3;
- 430) laminin receptor — MMP 7;
- 431) laminin receptor — MMP 9;
- 10 432) laminin receptor — membrane type matrix metalloproteinase I;
- 433) laminin receptor — MMP 12;
- 434) laminin receptor — MMP 13;
- 435) laminin receptor — a tumor antigen;
- 436) seprase — a cathepsin type protease;
- 15 437) seprase — cathepsin D;
- 438) seprase — to cathepsin K;
- 439) seprase — cathepsin L;
- 440) seprase — cathepsin O;
- 441) seprase — fibroblast activation protein;
- 20 442) seprase — folate binding receptors;
- 443) seprase — gastrin/cholecystokinin type B receptor;
- 444) seprase — guanidinobenzoatase;
- 445) seprase — matipase;
- 446) seprase — melanocyte stimulating hormone receptor;

- 447) seprase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 448) seprase — norepinephrine transporters;
- 449) seprase — nucleoside transporter proteins;
- 5 450) seprase — peripheral benzodiazepam binding receptors;
- 451) seprase — seprase;
- 452) seprase — sigma receptors;
- 453) seprase — somatostatin receptors;
- 454) seprase — stromelysin 3;
- 10 455) seprase — trypsin;
- 456) seprase — MMP 1;
- 457) seprase — MMP 2;
- 458) seprase — MMP 3;
- 459) seprase — MMP 7;
- 15 460) seprase — MMP 9;
- 461) seprase — membrane type matrix metalloproteinase I;
- 462) seprase — MMP 12;
- 463) seprase — MMP 13;
- 464) seprase — a tumor antigen;
- 20 465) guanidinobenzoatase — a cathepsin type protease;
- 466) guanidinobenzoatase — cathepsin D;
- 467) guanidinobenzoatase — to cathepsin K;
- 468) guanidinobenzoatase — cathepsin L;
- 469) guanidinobenzoatase — cathepsin O;
- 25 470) guanidinobenzoatase — fibroblast activation protein;

- 471) guanidinobenzoatase — folate binding receptors;
- 472) guanidinobenzoatase — gastrin/cholecystokinin type B receptor;
- 473) guanidinobenzoatase — guanidinobenzoatase;
- 474) guanidinobenzoatase — matipase;
- 5 475) guanidinobenzoatase — melanocyte stimulating hormone
receptor;
- 476) guanidinobenzoatase — nitrobenzylthioinosine-binding receptors
or (nucleoside transporter);
- 477) guanidinobenzoatase — norepinephrine transporters;
- 10 478) guanidinobenzoatase — nucleoside transporter proteins;
- 479) guanidinobenzoatase — peripheral benzodiazepam binding
receptors;
- 480) guanidinobenzoatase — sigma receptors;
- 481) guanidinobenzoatase — somatostatin receptors;
- 15 482) guanidinobenzoatase — stromelysin 3;
- 483) guanidinobenzoatase — trypsin;
- 484) guanidinobenzoatase — MMP 1;
- 485) guanidinobenzoatase — MMP 2;
- 486) guanidinobenzoatase — MMP 3;
- 20 487) guanidinobenzoatase — MMP 7;
- 488) guanidinobenzoatase — MMP 9;
- 489) guanidinobenzoatase — membrane type matrix
metalloproteinase I;
- 490) guanidinobenzoatase — MMP 12;
- 25 491) guanidinobenzoatase — MMP 13;

- 492) guanidinobenzoate — a tumor antigen;
- 493) peripheral benzodiazepam binding receptors — a cathepsin type protease;
- 494) peripheral benzodiazepam binding receptors — cathepsin D;
- 5 495) peripheral benzodiazepam binding receptors — to cathepsin K;
- 496) peripheral benzodiazepam binding receptors — cathepsin L;
- 497) peripheral benzodiazepam binding receptors — cathepsin O;
- 498) peripheral benzodiazepam binding receptors — fibroblast activation protein;
- 10 499) peripheral benzodiazepam binding receptors — folate binding receptors;
- 500) peripheral benzodiazepam binding receptors — gastrin/cholecystokinin type B receptor;
- 501) peripheral benzodiazepam binding receptors —
- 15 guanidinobenzoate;
- 502) peripheral benzodiazepam binding receptors — matrilysin;
- 503) peripheral benzodiazepam binding receptors — melanocyte stimulating hormone receptor;
- 504) peripheral benzodiazepam binding receptors —
- 20 nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 505) peripheral benzodiazepam binding receptors — norepinephrine transporters;
- 506) peripheral benzodiazepam binding receptors — nucleoside
- 25 transporter proteins;

- 507) peripheral benzodiazepam binding receptors — peripheral benzodiazepam binding receptors;
- 508) peripheral benzodiazepam binding receptors — sigma receptors;
- 509) peripheral benzodiazepam binding receptors — somatostatin
5 receptors;
- 510) peripheral benzodiazepam binding receptors — stromelysin 3;
- 511) peripheral benzodiazepam binding receptors — trypsin;
- 512) peripheral benzodiazepam binding receptors — MMP 1;
- 513) peripheral benzodiazepam binding receptors — MMP 2;
- 10 514) peripheral benzodiazepam binding receptors — MMP 3;
- 515) peripheral benzodiazepam binding receptors — MMP 7;
- 516) peripheral benzodiazepam binding receptors — MMP 9;
- 517) peripheral benzodiazepam binding receptors — membrane type matrix metalloproteinase I;
- 15 518) peripheral benzodiazepam binding receptors — MMP 12;
- 519) peripheral benzodiazepam binding receptors — MMP 13;
- 520) peripheral benzodiazepam binding receptors — a tumor antigen;
- 521) folate binding receptors — a cathepsin type protease;
- 522) folate binding receptors — cathepsin D;
- 20 523) folate binding receptors — to cathepsin K;
- 524) folate binding receptors — cathepsin L;
- 525) folate binding receptors — cathepsin O;
- 526) folate binding receptors — fibroblast activation protein;
- 527) folate binding receptors — folate binding receptors;
- 25 528) folate binding receptors — matrilysin;

- 529) folate binding receptors — melanocyte stimulating hormone receptor;
- 530) folate binding receptors — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 5 531) folate binding receptors — norepinephrine transporters;
- 532) folate binding receptors — nucleoside transporter proteins;
- 533) folate binding receptors — sigma receptors;
- 534) folate binding receptors — somatostatin receptors;
- 535) folate binding receptors — stromelysin 3;
- 10 536) folate binding receptors — trypsin;
- 537) folate binding receptors — MMP 1;
- 538) folate binding receptors — MMP 2;
- 539) folate binding receptors — MMP 3;
- 540) folate binding receptors — MMP 7;
- 15 541) folate binding receptors — MMP 9;
- 542) folate binding receptors — membrane type matrix metalloproteinase I;
- 543) folate binding receptors — MMP 12;
- 544) folate binding receptors — MMP 13;
- 20 545) folate binding receptors — a tumor antigen;
- 546) folate binding receptors — a cathepsin type protease;
- 547) folate binding receptors — cathepsin D;
- 548) folate binding receptors — to cathepsin K;
- 549) folate binding receptors — cathepsin L;
- 25 550) folate binding receptors — cathepsin O;

- 551) folate binding receptors — fibroblast activation protein;
- 552) folate binding receptors — folate binding receptors;
- 553) folate binding receptors — matripase;
- 554) folate binding receptors — melanocyte stimulating hormone
5 receptor;
- 555) folate binding receptors — nitrobenzylthioinosine-binding receptors
or (nucleoside transporter);
- 556) folate binding receptors — norepinephrine transporters;
- 557) folate binding receptors — nucleoside transporter proteins;
- 10 558) folate binding receptors — sigma receptors;
- 559) folate binding receptors — somatostatin receptors;
- 560) folate binding receptors — stromelysin 3;
- 561) folate binding receptors — trypsin;
- 562) folate binding receptors — MMP 1;
- 15 563) folate binding receptors — MMP 2;
- 564) folate binding receptors — MMP 3;
- 565) folate binding receptors — MMP 7;
- 566) folate binding receptors — MMP 9;
- 567) folate binding receptors — membrane type matrix
20 metalloproteinase I;
- 568) folate binding receptors — MMP 12;
- 569) folate binding receptors — MMP 13;
- 570) folate binding receptors — a tumor antigen;
- 571) nucleoside transporter proteins — a cathepsin type protease;
- 25 572) nucleoside transporter proteins — cathepsin D;

- 573) nucleoside transporter proteins — to cathepsin K;
- 574) nucleoside transporter proteins — cathepsin L;
- 575) nucleoside transporter proteins — cathepsin O;
- 576) nucleoside transporter proteins — fibroblast activation protein;
- 5 577) nucleoside transporter proteins — nucleoside transporter proteins;
- 578) nucleoside transporter proteins — matrilysin;
- 579) nucleoside transporter proteins — melanocyte stimulating
hormone receptor;
- 580) nucleoside transporter proteins — nitrobenzylthioinosine-binding
10 receptors or (nucleoside transporter);
- 581) nucleoside transporter proteins — norepinephrine transporters;
- 582) nucleoside transporter proteins — nucleoside transporter proteins;
- 583) nucleoside transporter proteins — sigma receptors;
- 584) nucleoside transporter proteins — somatostatin receptors;
- 15 585) nucleoside transporter proteins — stromelysin 3;
- 586) nucleoside transporter proteins — trypsin;
- 587) nucleoside transporter proteins — MMP 1;
- 588) nucleoside transporter proteins — MMP 2;
- 589) nucleoside transporter proteins — MMP 3;
- 20 590) nucleoside transporter proteins — MMP 7;
- 591) nucleoside transporter proteins — MMP 9;
- 592) nucleoside transporter proteins — membrane type matrix
metalloproteinase 1;
- 593) nucleoside transporter proteins — MMP 12;
- 25 594) nucleoside transporter proteins — MMP 13;

- 595) nucleoside transporter proteins — a tumor antigen;
- 596) melanocyte stimulating hormone receptor — a cathepsin type protease;
- 597) melanocyte stimulating hormone receptor — cathepsin D;
- 5 598) melanocyte stimulating hormone receptor — to cathepsin K;
- 599) melanocyte stimulating hormone receptor — cathepsin L;
- 600) melanocyte stimulating hormone receptor — cathepsin O;
- 601) melanocyte stimulating hormone receptor — fibroblast activation protein;
- 10 602) melanocyte stimulating hormone receptor — melanocyte stimulating hormone receptor;
- 603) melanocyte stimulating hormone receptor — melanocyte stimulating hormone receptor;
- 604) melanocyte stimulating hormone receptor —
- 15 nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 605) melanocyte stimulating hormone receptor — norepinephrine transporters;
- 606) melanocyte stimulating hormone receptor — nucleoside
- 20 transporter proteins;
- 607) melanocyte stimulating hormone receptor — sigma receptors;
- 608) melanocyte stimulating hormone receptor — somatostatin receptors;
- 609) melanocyte stimulating hormone receptor — stromelysin 3;
- 25 610) melanocyte stimulating hormone receptor — trypsin;

- 611) melanocyte stimulating hormone receptor — MMP 1;
- 612) melanocyte stimulating hormone receptor — MMP 2;
- 613) melanocyte stimulating hormone receptor — MMP 3;
- 614) melanocyte stimulating hormone receptor — MMP 7;
- 5 615) melanocyte stimulating hormone receptor — MMP 9;
- 616) melanocyte stimulating hormone receptor — membrane type
matrix metalloproteinase I;
- 617) melanocyte stimulating hormone receptor — MMP 12;
- 618) melanocyte stimulating hormone receptor — MMP 13;
- 10 619) melanocyte stimulating hormone receptor — a tumor antigen;
- 620) sigma receptors — a cathepsin type protease;
- 621) sigma receptors — cathepsin D;
- 622) sigma receptors — to cathepsin K;
- 623) sigma receptors — cathepsin L;
- 15 624) sigma receptors — cathepsin O;
- 625) sigma receptors — fibroblast activation protein;
- 626) sigma receptors — sigma receptors;
- 627) sigma receptors — matipase;
- 628) sigma receptors — norepinephrine transporters;
- 20 629) sigma receptors — sigma receptors;
- 630) sigma receptors — somatostatin receptors;
- 631) sigma receptors — stromelysin 3;
- 632) sigma receptors — trypsin;
- 633) sigma receptors — MMP 1;
- 25 634) sigma receptors — MMP 2;

- 635) sigma receptors — MMP 3;
- 636) sigma receptors — MMP 7;
- 637) sigma receptors — MMP 9;
- 638) sigma receptors — membrane type matrix metalloproteinase I;
- 5 639) sigma receptors — MMP 12;
- 640) sigma receptors — MMP 13;
- 641) sigma receptors — a tumor antigen ;
- 642) somatostatin receptors — a cathepsin type protease;
- 643) somatostatin receptors — cathepsin D;
- 10 644) somatostatin receptors — to cathepsin K;
- 645) somatostatin receptors — cathepsin L;
- 646) somatostatin receptors — cathepsin O;
- 647) somatostatin receptors — fibroblast activation protein;
- 648) somatostatin receptors — somatostatin receptors;
- 15 649) somatostatin receptors — matipase;
- 650) somatostatin receptors — melanocyte stimulating hormone
receptor;
- 651) somatostatin receptors — sigma receptors;
- 652) somatostatin receptors — somatostatin receptors;
- 20 653) somatostatin receptors — stromelysin 3;
- 654) somatostatin receptors — trypsin;
- 655) somatostatin receptors — MMP 1;
- 656) somatostatin receptors — MMP 2;
- 657) somatostatin receptors — MMP 3;
- 25 658) somatostatin receptors — MMP 7;

- 659) somatostatin receptors — MMP 9;
- 660) somatostatin receptors — membrane type matrix metalloproteinase I;
- 661) somatostatin receptors — MMP 12;
- 5 662) somatostatin receptors — MMP 13;
- 663) somatostatin receptors — a tumor antigen;
- 664) stromelysin 3 — a cathepsin type protease;
- 665) stromelysin 3 — cathepsin D;
- 666) stromelysin 3 — to cathepsin K;
- 10 667) stromelysin 3 — cathepsin L;
- 668) stromelysin 3 — cathepsin O;
- 669) stromelysin 3 — fibroblast activation protein;
- 670) stromelysin 3 — stromelysin 3;
- 671) stromelysin 3 — matipase;
- 15 672) stromelysin 3 — melanocyte stimulating hormone receptor;
- 673) stromelysin 3 — somatostatin receptors;
- 674) stromelysin 3 — trypsin;
- 675) stromelysin 3 — MMP 1;
- 676) stromelysin 3 — MMP 2;
- 20 677) stromelysin 3 — MMP 3;
- 678) stromelysin 3 — MMP 7;
- 679) stromelysin 3 — MMP 9;
- 680) stromelysin 3 — membrane type matrix metalloproteinase I;
- 681) stromelysin 3 — MMP 12;
- 25 682) stromelysin 3 — MMP 13;

- 683) stromelysin 3 — a tumor antigen;
- 684) trypsin — a cathepsin type protease;
- 685) trypsin — cathepsin D;
- 686) trypsin — to cathepsin K;
- 5 687) trypsin — cathepsin L;
- 688) trypsin — cathepsin O;
- 689) trypsin — fibroblast activation protein;
- 690) trypsin — trypsin;
- 691) trypsin — matipase;
- 10 692) trypsin — melanocyte stimulating hormone receptor;
- 693) trypsin — stromelysin 3;
- 694) trypsin — MMP 1;
- 695) trypsin — MMP 2;
- 696) trypsin — MMP 3;
- 15 697) trypsin — MMP 7;
- 698) trypsin — MMP 9;
- 699) trypsin — membrane type matrix metalloproteinase I;
- 700) trypsin — MMP 12;
- 701) trypsin — MMP 13;
- 20 702) trypsin — a tumor antigen;
- 703) MMP 1 — a cathepsin type protease;
- 704) MMP 1 — cathepsin D;
- 705) MMP 1 — to cathepsin K;
- 706) MMP 1 — cathepsin L;
- 25 707) MMP 1 — cathepsin O;

- 708) MMP 1 — fibroblast activation protein;
709) MMP 1 — matipase;
710) MMP 1 — melanocyte stimulating hormone receptor;
711) MMP 1 — stromelysin 3;
5 712) MMP 1 — MMP 1;
713) MMP 1 — MMP 2;
714) MMP 1 — MMP 3;
715) MMP 1 — MMP 7;
716) MMP 1 — MMP 9;
10 717) MMP 1 — membrane type matrix metalloproteinase I;
718) MMP 1 — MMP 12;
719) MMP 1 — MMP 13;
720) MMP 1 — a tumor antigen;
721) MMP-2 — a cathepsin type protease;
15 722) MMP-2 — cathepsin D;
723) MMP-2 — to cathepsin K;
724) MMP-2 — cathepsin L;
725) MMP-2 — cathepsin O;
726) MMP-2 — fibroblast activation protein;
20 727) MMP-2 — matipase;
728) MMP-2 — melanocyte stimulating hormone receptor;
729) MMP-2 — stromelysin 3;
730) MMP-2 — MMP 2;
731) MMP-2 — MMP 3;
25 732) MMP-2 — MMP 7;

- 733) MMP-2 — MMP 9;
- 734) MMP-2 — membrane type matrix metalloproteinase I;
- 735) MMP-2 — MMP-2;
- 736) MMP-2 — MMP-3;
- 5 737) MMP-2 — a tumor antigen;
- 738) MMP-3 — a cathepsin type protease;
- 739) MMP-3 — cathepsin D;
- 740) MMP-3 — to cathepsin K;
- 741) MMP-3 — cathepsin L;
- 10 742) MMP-3 — cathepsin O;
- 743) MMP-3 — matipase;
- 744) MMP-3 — MMP 3;
- 745) MMP-3 — MMP 7;
- 746) MMP-3 — MMP 9;
- 15 747) MMP-3 — membrane type matrix metalloproteinase I;
- 748) MMP-3 — MMP-3;
- 749) MMP-3 — a tumor antigen;
- 750) MMP 7 — a cathepsin type protease;
- 751) MMP 7 — cathepsin D;
- 20 752) MMP 7 — to cathepsin K;
- 753) MMP 7 — cathepsin L;
- 754) MMP 7 — cathepsin O;
- 755) MMP 7 — fibroblast activation protein;
- 756) MMP 7 — matipase;
- 25 757) MMP 7 — stromelysin 3;

- 758) MMP 7 — MMP 7;
- 759) MMP 7 — MMP 9;
- 760) MMP 7 — membrane type matrix metalloproteinase I;
- 761) MMP 7 — a tumor antigen;
- 5 762) MMP 9 — a cathepsin type protease;
- 763) MMP 9 — cathepsin D;
- 764) MMP 9 — to cathepsin K;
- 765) MMP 9 — cathepsin L;
- 766) MMP 9 — cathepsin O;
- 10 767) MMP 9 — matipase;
- 768) MMP 9 — MMP 9;
- 769) MMP 9 — membrane type matrix metalloproteinase I;
- 770) MMP 9 — a tumor antigen;
- 771) MMP 12 — a cathepsin type protease;
- 15 772) MMP 12 — cathepsin D;
- 773) MMP 12 — to cathepsin K;
- 774) MMP 12 — cathepsin L;
- 775) MMP 12 — cathepsin O;
- 776) MMP 12 — matipase;
- 20 777) MMP 12 — MMP 2;
- 778) MMP 12 — membrane type matrix metalloproteinase I;
- 779) MMP 12 — a tumor antigen;
- 780) MMP 13 — a cathepsin type protease;
- 781) MMP 13 — cathepsin D;
- 25 782) MMP 13 — to cathepsin K;

- 783) MMP 13 — cathepsin L;
- 784) MMP 13 — cathepsin O;
- 785) MMP 13 — matipase;
- 786) MMP 13 — membrane type matrix metalloproteinase I;
- 5 787) MMP 13 — a tumor antigen;
- 788) Membrane type matrix metalloproteinase — a cathepsin type
protease;
- 789) Membrane type matrix metalloproteinase — cathepsin D;
- 790) Membrane type matrix metalloproteinase — to cathepsin K;
- 10 791) Membrane type matrix metalloproteinase — cathepsin L;
- 792) Membrane type matrix metalloproteinase — cathepsin O;
- 793) Membrane type matrix metalloproteinase — matipase;
- 794) Membrane type matrix metalloproteinase — membrane type matrix
metalloproteinase I;
- 15 795) and Membrane type matrix metalloproteinase — a tumor antigen.

In preferred embodiments of (embodiments TLP #.X, wherein X=1, 2, 3,... 795),
the structure of the respective targeting ligands are of embodiments TL#Z
(wherein Z= 1, 2, 3...44) or as described in the targeting ligand neoantigen
20 sections of this document.

The scope of the present invention includes a compound comprised of one of
the pairs of tumor targeting ligands listed above and an effector agent with anti-
cancer activity.

In a preferred embodiment, ET is comprised of a third targeting receptor that is enriched on a tumor cell and a pair of targeting receptors selected from the list above. In a preferred embodiment this third targeting receptor binds to PSMA.

- 5 In preferred embodiments (designated 0.neoA) the compound ET is an anti-cancer drug comprised of at least one targeting ligand that is increased on a tumor cell compared to a normal cell and an effector agent that can irreversibly chemically modify a component of tumors that is also increased at a tumor cell compared to a normal cell. In a preferred embodiment (designated 1.neoA) the
10 number of targeting ligands is one. In a preferred embodiment (designated 2.neoA) the number of targeting ligands is two. In a preferred embodiment (designated 3.neoA) the number of targeting ligands is three. These compounds are useful in the method of target neoantigen immunotherapy described in a latter section of this document.

15

- In a preferred embodiment of the above embodiments, (0.neoA and 1neoA and 2.neoA, and 3.neoA); the tumor component that can be irreversibly modified is Prostate Specific Antigen, or Human glandular kallikrein 2, or Prostatic acid phosphatase, or Plasmin, or Placental type alkaline phosphatase, or Matritase,
20 or A Matrix metalloproteinases, or Thymidine phosphorylase, or Trypsin, or Urokinase, or Fatty Acid Synthase, or Steroid sulfatase, or Epidermal growth factor receptors, or Mitogen activated protein kinase kinase, or Phosphatidylinositol 3-kinase, or Mitogen activated protein kinase, or an Estrogen receptor, or Thymidylate synthase, or Protein kinase A, or Fibroblast
25 activation protein or seprase, or P-glycoprotein, or Ribonucleotide diphosphate

reductase, or Dihydrofolate reductase, or Src Kinases, or Platelet-derived growth factor receptors, or MMP 7, or MMP 1, or MMP 2, or MMP 3, or MMP 9, or MMP 12, or MMP 13, or Membrane type MMP 1, or A Cathepsin, or Cathepsin B, or Glutathione S -Transferases.

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In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Prostate Specific Antigen.

- 10 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Human glandular kallikrein 2.

- 15 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Prostatic acid phosphatase.

- 20 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Plasmin.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Placental type alkaline phosphatase.

25

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Matriptase.

- 5 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify A Matrix metalloproteinases.

- 10 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Thymidine phosphorylase.

- 15 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Trypsin.

- 20 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Urokinase.

- In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Fatty Acid Synthase.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Steroid sulfatase.

- 5 In a preferred embodiment, (embodiment TLP #.X, for X=1,2,3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Epidermal growth factor receptors.

- 10 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Mitogen activated protein kinase kinase.

- 15 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Phosphatidylinositol.

- 20 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify 3-kinase.

- In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Mitogen activated protein kinase.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify an Estrogen receptor.

- 5 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Thymidylate synthase.

- 10 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Protein kinase A.

- 15 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Fibroblast activation protein or seprase.

- 20 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify P-glycoprotein.

- In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Ribonucleotide diphosphate reductase.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Dihydrofolate reductase.

- 5 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Src Kinases.

- 10 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Platelet-derived growth factor receptors.

- 15 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify MMP 7:

- In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify MMP 1.

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- In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify MMP 2.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify MMP 3.

5 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify MMP 9.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
10 effector agent is comprised of a group that can irreversibly chemically modify MMP 12.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify
15 MMP 13.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify
Membrane type MMP 1.

20

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify a cathepsin.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Cathepsin B.

- 5 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a group that can irreversibly chemically modify Glutathione S –Transferases.

In a preferred embodiment ET is an anti-cancer drug comprised of a pair of
10 targeting ligands that bind to a pair of targeting receptors (a1 — a2) listed above or a pair of said targeting ligands and a third tumor-selective targeting ligand; and wherein the effector agents are comprised of one or more cytotoxic agents selected from the following list:

1. anthracyclines
- 15 2. ellipticines
3. mitoxantrones
4. bleomycins
5. taxols
6. inhibitors of thymidylate synthase
- 20 7. hydroxystaurosporine
8. cryptophycin analogs
9. vincristine
10. vinblastine
11. indanocene
- 25 12. mitomycin c

13. phosphoramidate mustard analogs
14. podophyllotoxins
15. ecteinascidins
16. didemnin
- 5 17. BW1843U89
18. 2-pyrrolinodoxorubicin
19. phthalascidin
20. an inhibitor of glycinamide ribonucleotide transformylase
21. an inhibitor hypoxanthine-guanine phosphoribosyltransferase
- 10 22. camptothecin
23. trimetrexate
24. a nucleoside transporter inhibitor
25. mycophenolic acid
26. an inhibitor of dihydroorotic acid dehydrogenase
- 15 27. an inhibitor to Orotidine 5'-phosphate decarboxylase
28. a radionuclide

In a preferred embodiment, of the above the embodiment, the number of anti-cancer drugs from the list that comprises E is 1, or 2.

- 20 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of anthracyclines.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of ellipticines.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of mitoxantrones.

5 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of Bleomycin.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of taxol.

10 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of an inhibitor of thymidylate synthase.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of Hydroxystaurosporine.

15 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a cryptophycin analogs.

20 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of Vincristine.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of Vinblastine.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of Indanocene.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
5 effector agent is comprised of mitomycin c.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a phosphoramidate mustard analogs.

10 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of Podophyllotoxins.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of Ecteinascidins.

15

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a Didemnin.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
20 effector agent is comprised of BW1843U89.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of 2-pyrrolinodoxorubicin.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a Phthalascidin.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
5 effector agent is comprised of an inhibitor of glycinamide ribonucleotide
transformylase.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
effector agent is comprised of an inhibitor hypoxanthene-guanine
10 phosphoribosyltransferase.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
effector agent is comprised of Campothecin.

15 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
effector agent is comprised of Trimetrexate.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
effector agent is comprised of a nucleoside transporter inhibitor.

20

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the
effector agent is comprised of mycophenolic acid.

In a preferred embodiment, (embodiment TLP #.X, for X=1,2,3,... 795) the
25 effector agent is comprised of an inhibitor of dihydroorotic acid dehydrogenase.

In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of an inhibitor to Orotidine 5'-phosphate decarboxylase.

- 5 In a preferred embodiment, of (embodiment TLP #.X, for X=1, 2, 3,... 795) the effector agent is comprised of a radionuclide.

In preferred embodiments;

- 10 (referred to as embodiments "OSTLP #X", for X=1,2,3,4....40 wherein X is the number of the targeting receptor in the list below);

- E1T1 and E2T2 are a set of anti-cancer drugs for use together, wherein E1 and E2 are effector agents that exhibit synergistic toxicity to a cell; and wherein T1
15 comprises a targeting ligand that binds to a first target receptor and T2 comprises a second targeting ligand that binds to the second target receptor, which is increased on a tumor cell compared to a normal cell and where the first targeting ligand binds to a targeting receptor selected from the following list:

- 1) a cathepsin type protease
- 20 2) a collagenase
- 3) a gelatinase
- 4) a matrix metalloproteinase
- 5) a membrane type matrix metalloproteinase
- 6) alpha v beta 3 integrin
- 25 7) bombesin /gastrin releasing peptide receptors

- | | | |
|----|-----|--|
| | 8) | cathepsin B |
| | 9) | cathepsin D |
| | 10) | cathepsin K |
| | 11) | cathepsin L |
| 5 | 12) | cathepsin O |
| | 13) | fibroblast activation protein |
| | 14) | folate binding receptors |
| | 15) | gastrin/cholecystokinin type B receptor |
| | 16) | glutamate carboxypeptidase II or (PSMA) |
| 10 | 17) | guanidinobenzoate |
| | 18) | laminin receptor |
| | 19) | matrilysin or |
| | 20) | matripase |
| | 21) | melanocyte stimulating hormone receptor |
| 15 | 22) | nitrobenzylthioinosine-binding receptors |
| | 23) | norepinephrine transporters |
| | 24) | nucleoside transporter proteins |
| | 25) | peripheral benzodiazepam binding receptors |
| | 26) | plasmin |
| 20 | 27) | seprase |
| | 28) | sigma receptors |
| | 29) | somatostatin receptors |
| | 30) | stromelysin 3 |
| | 31) | trypsin |
| 25 | 32) | urokinase |

- 33) MMP 1
- 34) MMP 2
- 35) MMP 3
- 36) MMP 7
- 5 37) MMP 9
- 38) Membrane type matrix metalloproteinase I
- 39) MMP 12
- 40) MMP 13

- 10 In preferred embodiments; of embodiments (OSTLP #X, for X=1, 2, 3, 4....40);
- The effector agent E1 inhibits the denovo synthesis of a biomolecule(s) that is necessary for cell replication and or survival, and the effector agent E2 inhibits a salvage pathway(s) that can enable a cell to by-pass the metabolic block caused by E1. In a preferred embodiment of these embodiments, E1 inhibits
- 15 nucleoside synthesis and E2 inhibits nucleoside uptake.

In preferred embodiments of the above embodiments, E1 is comprised of an inhibitor to one or more of the following enzymes:

- 1.) thymidylate synthase
- 20 2.) ribonucleotide reductase
- 3.) glycinamide ribonucleotide transformylase
- 4.) 5-aminoimidazole-4-carboxamide ribonucleotide transferase
- 5.) dihydroorotate dehydrogenase
- 6.) carbamoyl phosphate synthetase
- 25 7.) orotidine-5'-phosphate decarboxylase

8.) inosine 5'monophosphate dehydrogenase

9.) aspartate transcarbamylase

and E2 is comprised of an inhibitor to one or more of the following enzymes:

- 5 1.) nucleoside transporter proteins
- 2.) thymidine kinase
- 3.) uridine/cytidine kinase
- 4.) deoxycytidine kinase
- 5.) deoxyguanosine kinase
- 10 6.) hypoxanthine-guanine phosphoribosyltransferase
- 7.) xanthine-guanine phosphoribosyltransferase
- 8.) adenine phosphoribosyltransferase

In preferred embodiments:

- 15 designated: (embodiment "1STLP #.X", wherein X is the number given below to the pairs of target receptors and X=1, 2, 3,... 795);

E1T1 and E2T2 are a set of anti-cancer drugs for use together, wherein E1 and E2 exhibit synergistic toxicity to a cell; and wherein T1 comprises a targeting
20 ligand that binds to the first target receptor (a1); and T2 comprises a second targeting ligand that binds to the second target receptor (a2) indicated in the pairs of (a1 — a2) listed below:

- 1) urokinase — a cathepsin type protease;
- 25 2) urokinase — a collagenase;

- 3) urokinase — a gelatinase;
- 4) urokinase — a matrix metalloproteinase;
- 5) urokinase — a membrane type matrix metalloproteinase;
- 6) urokinase — alpha v beta 3 integrin;
- 5 7) urokinase — bombesin /gastrin releasing peptide receptors;
- 8) urokinase — cathepsin B;
- 9) urokinase — cathepsin D;
- 10) urokinase — to cathepsin K;
- 11) urokinase — cathepsin L;
- 10 12) urokinase — cathepsin O;
- 13) urokinase — fibroblast activation protein;
- 14) urokinase — folate binding receptors;
- 15) urokinase — gastrin/cholecystokinin type B receptor;
- 16) urokinase — glutamate carboxypeptidase II or (PSMA);
- 15 17) urokinase — guanidinobenzoatase;
- 18) urokinase — laminin receptor;
- 19) urokinase — matrilysin;
- 20) urokinase — matripase;
- 21) urokinase — melanocyte stimulating hormone receptor;
- 20 22) urokinase — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
- 23) urokinase — norepinephrine transporters;
- 24) urokinase — nucleoside transporter proteins;
- 25) urokinase — peripheral benzodiazepam binding receptors;
- 25 26) urokinase — plasmin;

- 27) urokinase — seprase;
- 28) urokinase — sigma receptors;
- 29) urokinase — somatostatin receptors;
- 30) urokinase — stromelysin 3;
- 5 31) urokinase — trypsin;
- 32) urokinase — urokinase;
- 33) urokinase — MMP 1;
- 34) urokinase — MMP 2;
- 35) urokinase — MMP 3;
- 10 36) urokinase — MMP 7;
- 37) urokinase — MMP 9;
- 38) urokinase — membrane type matrix metalloproteinase I;
- 39) urokinase — MMP 12;
- 40) urokinase — MMP 13;
- 15 41) urokinase — a tumor antigen;
- 42) plasmin — a cathepsin type protease;
- 43) plasmin — a collagenase;
- 44) plasmin — a gelatinase;
- 45) plasmin — a matrix metalloproteinase;
- 20 46) plasmin — a membrane type matrix metalloproteinase;
- 47) plasmin — alpha v beta 3 integrin;
- 48) plasmin — bombesin /gastrin releasing peptide receptors;
- 49) plasmin — cathepsin B;
- 50) plasmin — cathepsin D;
- 25 51) plasmin — to cathepsin K;

- 52) plasmin — cathepsin L;
- 53) plasmin — cathepsin O;
- 54) plasmin — fibroblast activation protein;
- 55) plasmin — folate binding receptors;
- 5 56) plasmin — gastrin/cholecystokinin type B receptor;
- 57) plasmin — glutamate carboxypeptidase II or (PSMA);
- 58) plasmin — guanidinobenzoate;
- 59) plasmin — laminin receptor;
- 60) plasmin — matrilysin;
- 10 61) plasmin — matrilysin;
- 62) plasmin — melanocyte stimulating hormone receptor;
- 63) plasmin — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 64) plasmin — norepinephrine transporters;
- 15 65) plasmin — nucleoside transporter proteins;
- 66) plasmin — peripheral benzodiazepam binding receptors;
- 67) plasmin — plasmin;
- 68) plasmin — seprase;
- 69) plasmin — sigma receptors;
- 20 70) plasmin — somatostatin receptors;
- 71) plasmin — stromelysin 3;
- 72) plasmin — trypsin;
- 73) plasmin — urokinase;
- 74) plasmin — MMP 1;
- 25 75) plasmin — MMP 2;

- 76) plasmin — MMP 3;
- 77) plasmin — MMP 7;
- 78) plasmin — MMP 9;
- 79) plasmin — membrane type matrix metalloproteinase I;
- 5 80) plasmin — MMP 12;
- 81) plasmin — MMP 13;
- 82) plasmin — a tumor antigen;
- 83) a collagenase — a cathepsin type protease;
- 84) a collagenase — a collagenase;
- 10 85) a collagenase — a gelatinase;
- 86) a collagenase — a matrix metalloproteinase;
- 87) a collagenase — a membrane type matrix metalloproteinase;
- 88) a collagenase — alpha v beta 3 integrin;
- 89) a collagenase — bombesin /gastrin releasing peptide receptors;
- 15 90) a collagenase — cathepsin B;
- 91) a collagenase — cathepsin D;
- 92) a collagenase — to cathepsin K;
- 93) a collagenase — cathepsin L;
- 94) a collagenase — cathepsin O;
- 20 95) a collagenase — fibroblast activation protein;
- 96) a collagenase — folate binding receptors;
- 97) a collagenase — gastrin/cholecystokinin type B receptor;
- 98) a collagenase — glutamate carboxypeptidase II or (PSMA);
- 99) a collagenase — guanidinobenzoatase;
- 25 100) a collagenase — laminin receptor;

- 101) a collagenase — matrilysin;
- 102) a collagenase — matripase;
- 103) a collagenase — melanocyte stimulating hormone receptor;
- 104) a collagenase — nitrobenzylthiinosine-binding receptors or
5 (nucleoside transporter);
- 105) a collagenase — norepinephrine transporters;
- 106) a collagenase — nucleoside transporter proteins;
- 107) a collagenase — peripheral benzodiazepam binding receptors;
- 108) a collagenase — seprase;
- 10 109) a collagenase — sigma receptors;
- 110) a collagenase — somatostatin receptors;
- 111) a collagenase — stromelysin 3;
- 112) a collagenase — trypsin;
- 113) a collagenase — a collagenase;
- 15 114) a collagenase — MMP 1;
- 115) a collagenase — MMP 2;
- 116) a collagenase — MMP 3;
- 117) a collagenase — MMP 7;
- 118) a collagenase — MMP 9;
- 20 119) a collagenase — membrane type matrix metalloproteinase I;
- 120) a collagenase — MMP 12;
- 121) a collagenase — MMP 13;
- 122) a collagenase — a tumor antigen;
- 123) a gelatinase — a cathepsin type protease;
- 25 124) a gelatinase — a gelatinase;

- 125) a gelatinase — a matrix metalloproteinase;
- 126) a gelatinase — a membrane type matrix metalloproteinase;
- 127) a gelatinase — alpha v beta 3 integrin;
- 128) a gelatinase — bombesin /gastrin releasing peptide receptors;
- 5 129) a gelatinase — cathepsin B;
- 130) a gelatinase — cathepsin D;
- 131) a gelatinase — to cathepsin K;
- 132) a gelatinase — cathepsin L;
- 133) a gelatinase — cathepsin O;
- 10 134) a gelatinase — fibroblast activation protein;
- 135) a gelatinase — folate binding receptors;
- 136) a gelatinase — gastrin/cholecystokinin type B receptor;
- 137) a gelatinase — glutamate carboxypeptidase II or (PSMA);
- 138) a gelatinase — guanidinobenzoatase;
- 15 139) a gelatinase — laminin receptor;
- 140) a gelatinase — matrilysin;
- 141) a gelatinase — matripase;
- 142) a gelatinase — melanocyte stimulating hormone receptor;
- 143) a gelatinase — nitrobenzylthioinosine-binding receptors or
- 20 (nucleoside transporter);
- 144) a gelatinase — norepinephrine transporters;
- 145) a gelatinase — nucleoside transporter proteins;
- 146) a gelatinase — peripheral benzodiazepam binding receptors;
- 147) a gelatinase — seprase;
- 25 148) a gelatinase — sigma receptors;

- 149) a gelatinase — somatostatin receptors;
- 150) a gelatinase — stromelysin 3;
- 151) a gelatinase — trypsin;
- 152) a gelatinase — MMP 1;
- 5 153) a gelatinase — MMP 2;
- 154) a gelatinase — MMP 3;
- 155) a gelatinase — MMP 7;
- 156) a gelatinase — MMP 9;
- 157) a gelatinase — membrane type matrix metalloproteinase I;
- 10 158) a gelatinase — MMP 12;
- 159) a gelatinase — MMP 13;
- 160) a gelatinase — a tumor antigen;
- 161) a matrix metalloproteinase — a cathepsin type protease;
- 162) a matrix metalloproteinase — a collagenase;
- 15 163) a matrix metalloproteinase — a gelatinase;
- 164) a matrix metalloproteinase — a matrix metalloproteinase;
- 165) a matrix metalloproteinase — a membrane type matrix
metalloproteinase;
- 166) a matrix metalloproteinase — alpha v beta 3 integrin;
- 20 167) a matrix metalloproteinase — bombesin /gastrin releasing peptide
receptors;
- 168) a matrix metalloproteinase — cathepsin B;
- 169) a matrix metalloproteinase — cathepsin D;
- 170) a matrix metalloproteinase — to cathepsin K;
- 25 171) a matrix metalloproteinase — cathepsin L;

- 172) a matrix metalloproteinase — cathepsin O;
- 173) a matrix metalloproteinase — fibroblast activation protein;
- 174) a matrix metalloproteinase — folate binding receptors;
- 175) a matrix metalloproteinase — gastrin/cholecystokinin type B
5 receptor;
- 176) a matrix metalloproteinase — glutamate carboxypeptidase II or
(PSMA);
- 177) a matrix metalloproteinase — guanidinobenzoate;
- 178) a matrix metalloproteinase — laminin receptor;
- 10 179) a matrix metalloproteinase — matrilysin;
- 180) a matrix metalloproteinase — matrilysin;
- 181) a matrix metalloproteinase — melanocyte stimulating hormone
receptor;
- 182) a matrix metalloproteinase — nitrobenzylthioinosine-binding
15 receptors or (nucleoside transporter);
- 183) a matrix metalloproteinase — norepinephrine transporters;
- 184) a matrix metalloproteinase — nucleoside transporter proteins;
- 185) a matrix metalloproteinase — peripheral benzodiazepam binding
receptors;
- 20 186) a matrix metalloproteinase — plasmin;
- 187) a matrix metalloproteinase — seprase;
- 188) a matrix metalloproteinase — sigma receptors;
- 189) a matrix metalloproteinase — somatostatin receptors;
- 190) a matrix metalloproteinase — stromelysin 3;
- 25 191) a matrix metalloproteinase — trypsin;

- 192) a matrix metalloproteinase — a matrix metalloproteinase;
- 193) a matrix metalloproteinase — MMP 1;
- 194) a matrix metalloproteinase — MMP 2;
- 195) a matrix metalloproteinase — MMP 3;
- 5 196) a matrix metalloproteinase — MMP 7;
- 197) a matrix metalloproteinase — MMP 9;
- 198) a matrix metalloproteinase — membrane type matrix
metalloproteinase I;
- 199) a matrix metalloproteinase — MMP 12;
- 10 200) a matrix metalloproteinase — MMP 13;
- 201) a matrix metalloproteinase — a tumor antigen;
- 202) a membrane type metalloproteinase — a cathepsin type protease;
- 203) a membrane type metalloproteinase — a membrane type matrix
metalloproteinase;
- 15 204) a membrane type metalloproteinase — alpha v beta 3 integrin;
- 205) a membrane type metalloproteinase — bombesin /gastrin
releasing peptide receptors;
- 206) a membrane type metalloproteinase — cathepsin B;
- 207) a membrane type metalloproteinase — cathepsin D;
- 20 208) a membrane type metalloproteinase — to cathepsin K;
- 209) a membrane type metalloproteinase — cathepsin L;
- 210) a membrane type metalloproteinase — cathepsin O;
- 211) a membrane type metalloproteinase — fibroblast activation
protein;
- 25 212) a membrane type metalloproteinase — folate binding receptors;

- 213) a membrane type metalloproteinase — gastrin/cholecystokinin type B receptor;
- 214) a membrane type metalloproteinase — glutamate carboxypeptidase II or (PSMA);
- 5 215) a membrane type metalloproteinase — guanidinobenzoatase;
- 216) a membrane type metalloproteinase — laminin receptor;
- 217) a membrane type metalloproteinase — matrilysin;
- 218) a membrane type metalloproteinase — matripase;
- 219) a membrane type metalloproteinase — melanocyte stimulating hormone receptor;
- 10 220) a membrane type metalloproteinase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 221) a membrane type metalloproteinase — norepinephrine transporters;
- 15 222) a membrane type metalloproteinase — nucleoside transporter proteins;
- 223) a membrane type metalloproteinase — peripheral benzodiazepam binding receptors;
- 224) a membrane type metalloproteinase — seprase;
- 20 225) a membrane type metalloproteinase — sigma receptors;
- 226) a membrane type metalloproteinase — somatostatin receptors;
- 227) a membrane type metalloproteinase — stromelysin 3;
- 228) a membrane type metalloproteinase — trypsin;
- 229) a membrane type metalloproteinase — MMP 1;
- 25 230) a membrane type metalloproteinase — MMP 2;

- 231) a membrane type metalloproteinase — MMP 3;
- 232) a membrane type metalloproteinase — MMP 7;
- 233) a membrane type metalloproteinase — MMP 9;
- 234) a membrane type metalloproteinase — membrane type matrix
5 metalloproteinase I;
- 235) a membrane type metalloproteinase — MMP 12;
- 236) a membrane type metalloproteinase — MMP 13;
- 237) a membrane type metalloproteinase — a tumor antigen;
- 238) alpha v beta 3 Integrin — a cathepsin type protease;
- 10 239) alpha v beta 3 integrin — alpha v beta 3 integrin;
- 240) alpha v beta 3 integrin — bombesin /gastrin releasing peptide
receptors;
- 241) alpha v beta 3 integrin — cathepsin B;
- 242) alpha v beta 3 integrin — cathepsin D;
- 15 243) alpha v beta 3 integrin — cathepsin K;
- 244) alpha v beta 3 integrin — cathepsin L;
- 245) alpha v beta 3 integrin — cathepsin O;
- 246) alpha v beta 3 integrin — fibroblast activation protein;
- 247) alpha v beta 3 integrin — folate binding receptors;
- 20 248) alpha v beta 3 integrin — gastrin/cholecystokinin type B receptor;
- 249) alpha v beta 3 integrin — glutamate carboxypeptidase II or
(PSMA);
- 250) alpha v beta 3 integrin — guanidinobenzoatase;
- 251) alpha v beta 3 integrin — laminin receptor;
- 25 252) alpha v beta 3 integrin — matrilysin;

- 253) alpha v beta 3 integrin — matrilysin;
- 254) alpha v beta 3 integrin — melanocyte stimulating hormone
receptor;
- 255) alpha v beta 3 integrin — nitrobenzylthioinosine-binding receptors
5 or (nucleoside transporter);
- 256) alpha v beta 3 integrin — norepinephrine transporters;
- 257) alpha v beta 3 integrin — nucleoside transporter proteins;
- 258) alpha v beta 3 integrin — peripheral benzodiazepam binding
receptors;
- 10 259) alpha v beta 3 integrin — seprase;
- 260) alpha v beta 3 integrin — sigma receptors;
- 261) alpha v beta 3 integrin — somatostatin receptors;
- 262) alpha v beta 3 integrin — stromelysin 3;
- 263) alpha v beta 3 integrin — trypsin;
- 15 264) alpha v beta 3 integrin — MMP 1;
- 265) alpha v beta 3 integrin — MMP 2;
- 266) alpha v beta 3 integrin — MMP 3;
- 267) alpha v beta 3 integrin — MMP 7;
- 268) alpha v beta 3 integrin — MMP 9;
- 20 269) alpha v beta 3 integrin — membrane type
matrix metalloproteinase I;
- 270) alpha v beta 3 integrin — MMP 12;
- 271) alpha v beta 3 integrin — MMP 13;
- 272) alpha v beta 3 integrin — a tumor antigen;
- 25 273) cathepsin B — a cathepsin type protease;

- 274) cathepsin B — bombesin /gastrin releasing peptide receptors;
- 275) cathepsin B — cathepsin B;
- 276) cathepsin B — cathepsin D;
- 277) cathepsin B — to cathepsin K;
- 5 278) cathepsin B — cathepsin L;
- 279) cathepsin B — cathepsin O;
- 280) cathepsin B — fibroblast activation protein;
- 281) cathepsin B — folate binding receptors;
- 282) cathepsin B — gastrin/cholecystokinin type B receptor;
- 10 283) cathepsin B — glutamate carboxypeptidase II or (PSMA);
- 284) cathepsin B — guanidinobenzoate;
- 285) cathepsin B — laminin receptor;
- 286) cathepsin B — matrilysin;
- 287) cathepsin B — matrilysin;
- 15 288) cathepsin B — melanocyte stimulating hormone receptor;
- 289) cathepsin B — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
- 290) cathepsin B — norepinephrine transporters;
- 291) cathepsin B — nucleoside transporter proteins;
- 20 292) cathepsin B — peripheral benzodiazepam binding receptors;
- 293) cathepsin B — seprase;
- 294) cathepsin B — sigma receptors;
- 295) cathepsin B — somatostatin receptors;
- 296) cathepsin B — stromelysin 3;
- 25 297) cathepsin B — trypsin;

- 298) cathepsin B — MMP 1;
- 299) cathepsin B — MMP 2;
- 300) cathepsin B — MMP 3;
- 301) cathepsin B — MMP 7;
- 5 302) cathepsin B — MMP 9;
- 303) cathepsin B — membrane type matrix metalloproteinase I;
- 304) cathepsin B — MMP 12;
- 305) cathepsin B — MMP 13;
- 306) cathepsin B — a tumor antigen;
- 10 307) bombesin/gastrin releasing peptide receptors — a cathepsin type
protease;
- 308) bombesin/gastrin releasing peptide receptors — bombesin /gastrin
releasing peptide receptors;
- 309) bombesin/gastrin releasing peptide receptors — cathepsin B;
- 15 310) bombesin/gastrin releasing peptide receptors — cathepsin D;
- 311) bombesin/gastrin releasing peptide receptors — to cathepsin K;
- 312) bombesin/gastrin releasing peptide receptors — cathepsin L;
- 313) bombesin/gastrin releasing peptide receptors — cathepsin O;
- 314) bombesin/gastrin releasing peptide receptors — fibroblast
20 activation protein;
- 315) bombesin/gastrin releasing peptide receptors — folate binding
receptors;
- 316) bombesin/gastrin releasing peptide receptors —
gastrin/cholecystokinin type B receptor;

- 317) bombesin/gastrin releasing peptide receptors — glutamate carboxypeptidase II or (PSMA);
- 318) bombesin/gastrin releasing peptide receptors — guanidinobenzoate;
- 5 319) bombesin/gastrin releasing peptide receptors — laminin receptor;
- 320) bombesin/gastrin releasing peptide receptors — matrilysin;
- 321) bombesin/gastrin releasing peptide receptors — matrilysin;
- 322) bombesin/gastrin releasing peptide receptors — melanocyte stimulating hormone receptor;
- 10 323) bombesin/gastrin releasing peptide receptors — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 324) bombesin/gastrin releasing peptide receptors — norepinephrine transporters;
- 15 325) bombesin/gastrin releasing peptide receptors — nucleoside transporter proteins;
- 326) bombesin/gastrin releasing peptide receptors — peripheral benzodiazepam binding receptors;
- 327) bombesin/gastrin releasing peptide receptors — seprase;
- 20 328) bombesin/gastrin releasing peptide receptors — sigma receptors;
- 329) bombesin/gastrin releasing peptide receptors — somatostatin receptors;
- 330) bombesin/gastrin releasing peptide receptors — stromelysin 3;
- 331) bombesin/gastrin releasing peptide receptors — trypsin;
- 25 332) bombesin/gastrin releasing peptide receptors — MMP 1;

- 333) bombesin/gastrin releasing peptide receptors — MMP 2;
- 334) bombesin/gastrin releasing peptide receptors — MMP 3;
- 335) bombesin/gastrin releasing peptide receptors — MMP 7;
- 336) bombesin/gastrin releasing peptide receptors — MMP 9;
- 5 337) bombesin/gastrin releasing peptide receptors — membrane type
matrix metalloproteinase I;
- 338) bombesin/gastrin releasing peptide receptors — MMP 12;
- 339) bombesin/gastrin releasing peptide receptors — MMP 13;
- 340) bombesin/gastrin releasing peptide receptors — a tumor antigen;
- 10 341) fibroblast activation protein — a cathepsin type protease;
- 342) fibroblast activation protein — cathepsin D;
- 343) fibroblast activation protein — to cathepsin K;
- 344) fibroblast activation protein — cathepsin L;
- 345) fibroblast activation protein — cathepsin O;
- 15 346) fibroblast activation protein — fibroblast activation protein;
- 347) fibroblast activation protein — folate binding receptors;
- 348) fibroblast activation protein — gastrin/cholecystokinin type B
receptor;
- 349) fibroblast activation protein — glutamate carboxypeptidase II or
20 (PSMA);
- 350) fibroblast activation protein — guanidinobenzoatase;
- 351) fibroblast activation protein — laminin receptor;
- 352) fibroblast activation protein — matrilysin;
- 353) fibroblast activation protein — matripase;

- 354) fibroblast activation protein — melanocyte stimulating hormone receptor;
- 355) fibroblast activation protein — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 5 356) fibroblast activation protein — norepinephrine transporters;
- 357) fibroblast activation protein — nucleoside transporter proteins;
- 358) fibroblast activation protein — peripheral benzodiazepam binding receptors;
- 359) fibroblast activation protein — plasmin;
- 10 360) fibroblast activation protein — seprase;
- 361) fibroblast activation protein — sigma receptors;
- 362) fibroblast activation protein — somatostatin receptors;
- 363) fibroblast activation protein — stromelysin 3;
- 364) fibroblast activation protein — trypsin;
- 15 365) fibroblast activation protein — MMP 1;
- 366) fibroblast activation protein — MMP 2;
- 367) fibroblast activation protein — MMP 3;
- 368) fibroblast activation protein — MMP 7;
- 369) fibroblast activation protein — MMP 9;
- 20 370) fibroblast activation protein — membrane type matrix metalloproteinase I;
- 371) fibroblast activation protein — MMP 12;
- 372) fibroblast activation protein — MMP 13;
- 373) fibroblast activation protein — a tumor antigen;
- 25 374) glutamate carboxypeptidase II or PSMA — cathepsin D;

- 375) glutamate carboxypeptidase II or PSMA — to cathepsin K;
- 376) glutamate carboxypeptidase II or PSMA — cathepsin L;
- 377) glutamate carboxypeptidase II or PSMA — cathepsin O;
- 378) glutamate carboxypeptidase II or PSMA — fibroblast activation
5 protein;
- 379) glutamate carboxypeptidase II or PSMA — folate binding
receptors;
- 380) glutamate carboxypeptidase II or PSMA — gastrin/cholecystokinin
type B receptor;
- 10 381) glutamate carboxypeptidase II or PSMA — glutamate
carboxypeptidase II or (PSMA);
- 382) glutamate carboxypeptidase II or PSMA — guanidinobenzoate;
- 383) glutamate carboxypeptidase II or PSMA — laminin receptor;
- 384) glutamate carboxypeptidase II or PSMA — matrilysin;
- 15 385) glutamate carboxypeptidase II or PSMA — matrilysin;
- 386) glutamate carboxypeptidase II or PSMA — melanocyte stimulating
hormone receptor;
- 387) glutamate carboxypeptidase II or PSMA — nitrobenzylthioinosine-
binding receptors or (nucleoside transporter);
- 20 388) glutamate carboxypeptidase II or PSMA — nucleoside transporter
proteins;
- 389) glutamate carboxypeptidase II or PSMA — peripheral
benzodiazepam binding receptors;
- 390) glutamate carboxypeptidase II or PSMA — seprase;
- 25 391) glutamate carboxypeptidase II or PSMA — sigma receptors;

- 392) glutamate carboxypeptidase II or PSMA — somatostatin receptors;
- 393) glutamate carboxypeptidase II or PSMA — stromelysin 3;
- 394) glutamate carboxypeptidase II or PSMA — trypsin;
- 395) glutamate carboxypeptidase II or PSMA — MMP 1;
- 5 396) glutamate carboxypeptidase II or PSMA — MMP 2;
- 397) glutamate carboxypeptidase II or PSMA — MMP 3;
- 398) glutamate carboxypeptidase II or PSMA — MMP 7;
- 399) glutamate carboxypeptidase II or PSMA — MMP 9;
- 400) glutamate carboxypeptidase II or PSMA — membrane type matrix
- 10 metalloproteinase I;
- 401) glutamate carboxypeptidase II or PSMA — MMP 12;
- 402) glutamate carboxypeptidase II or PSMA — MMP 13;
- 403) glutamate carboxypeptidase II or PSMA — a tumor antigen;
- 404) laminin receptor — a cathepsin type protease;
- 15 405) laminin receptor — cathepsin B;
- 406) laminin receptor — cathepsin D;
- 407) laminin receptor — to cathepsin K;
- 408) laminin receptor — cathepsin L;
- 409) laminin receptor — cathepsin O;
- 20 410) laminin receptor — fibroblast activation protein;
- 411) laminin receptor — folate binding receptors;
- 412) laminin receptor — gastrin/cholecystokinin type B receptor;
- 413) laminin receptor — guanidinobenzoatase;
- 414) laminin receptor — laminin receptor;
- 25 415) laminin receptor — matrilysin;

- 416) laminin receptor — matrilysin;
417) laminin receptor — melanocyte stimulating hormone receptor;
418) laminin receptor — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
5 419) laminin receptor — norepinephrine transporters;
420) laminin receptor — nucleoside transporter proteins;
421) laminin receptor — peripheral benzodiazepam binding receptors;
422) laminin receptor — seprase;
423) laminin receptor — sigma receptors;
10 424) laminin receptor — somatostatin receptors;
425) laminin receptor — stromelysin 3;
426) laminin receptor — trypsin;
427) laminin receptor — MMP 1;
428) laminin receptor — MMP 2;
15 429) laminin receptor — MMP 3;
430) laminin receptor — MMP 7;
431) laminin receptor — MMP 9;
432) laminin receptor — membrane type matrix metalloproteinase I;
433) laminin receptor — MMP 12;
20 434) laminin receptor — MMP 13;
435) laminin receptor — a tumor antigen;
436) seprase — a cathepsin type protease;
437) seprase — cathepsin D;
438) seprase — to cathepsin K;
25 439) seprase — cathepsin L;

- 440) seprase — cathepsin O;
- 441) seprase — fibroblast activation protein;
- 442) seprase — folate binding receptors;
- 443) seprase — gastrin/cholecystokinin type B receptor;
- 5 444) seprase — guanidinobenzoatase;
- 445) seprase — matipase;
- 446) seprase — melanocyte stimulating hormone receptor;
- 447) seprase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 10 448) seprase — norepinephrine transporters;
- 449) seprase — nucleoside transporter proteins;
- 450) seprase — peripheral benzodiazepam binding receptors;
- 451) seprase — seprase;
- 452) seprase — sigma receptors;
- 15 453) seprase — somatostatin receptors;
- 454) seprase — stromelysin 3;
- 455) seprase — trypsin;
- 456) seprase — MMP 1;
- 457) seprase — MMP 2;
- 20 458) seprase — MMP 3;
- 459) seprase — MMP 7;
- 460) seprase — MMP 9;
- 461) seprase — membrane type matrix metalloproteinase I;
- 462) seprase — MMP 12;
- 25 463) seprase — MMP 13;

- 464) seprase — a tumor antigen;
- 465) guanidinobenzoatase — a cathepsin type protease;
- 466) guanidinobenzoatase — cathepsin D;
- 467) guanidinobenzoatase — to cathepsin K;
- 5 468) guanidinobenzoatase — cathepsin L;
- 469) guanidinobenzoatase — cathepsin O;
- 470) guanidinobenzoatase — fibroblast activation protein;
- 471) guanidinobenzoatase — folate binding receptors;
- 472) guanidinobenzoatase — gastrin/cholecystokinin type B receptor;
- 10 473) guanidinobenzoatase — guanidinobenzoatase;
- 474) guanidinobenzoatase — matripase;
- 475) guanidinobenzoatase — melanocyte stimulating hormone
receptor;
- 476) guanidinobenzoatase — nitrobenzylthioinosine-binding receptors
15 or (nucleoside transporter);
- 477) guanidinobenzoatase — norepinephrine transporters;
- 478) guanidinobenzoatase — nucleoside transporter proteins;
- 479) guanidinobenzoatase — peripheral benzodiazepam binding
receptors;
- 20 480) guanidinobenzoatase — sigma receptors;
- 481) guanidinobenzoatase — somatostatin receptors;
- 482) guanidinobenzoatase — stromelysin 3;
- 483) guanidinobenzoatase — trypsin;
- 484) guanidinobenzoatase — MMP 1;
- 25 485) guanidinobenzoatase — MMP 2;

- 486) guanidinobenzoatase — MMP 3;
- 487) guanidinobenzoatase — MMP 7;
- 488) guanidinobenzoatase — MMP 9;
- 489) guanidinobenzoatase — membrane type matrix
5 metalloproteinase I;
- 490) guanidinobenzoatase — MMP 12;
- 491) guanidinobenzoatase — MMP 13;
- 492) guanidinobenzoatase — a tumor antigen;
- 493) peripheral benzodiazepam binding receptors — a cathepsin type
10 protease;
- 494) peripheral benzodiazepam binding receptors — cathepsin D;
- 495) peripheral benzodiazepam binding receptors — to cathepsin K;
- 496) peripheral benzodiazepam binding receptors — cathepsin L;
- 497) peripheral benzodiazepam binding receptors — cathepsin O;
- 15 498) peripheral benzodiazepam binding receptors — fibroblast
activation protein;
- 499) peripheral benzodiazepam binding receptors — folate binding
receptors;
- 500) peripheral benzodiazepam binding receptors —
20 gastrin/cholecystokinin type B receptor;
- 501) peripheral benzodiazepam binding receptors —
guanidinobenzoatase;
- 502) peripheral benzodiazepam binding receptors — matipase;
- 503) peripheral benzodiazepam binding receptors — melanocyte
25 stimulating hormone receptor;

- 504) peripheral benzodiazepam binding receptors —
nitrobenzylthioinosine-binding receptors or (nucleoside
transporter);
- 505) peripheral benzodiazepam binding receptors — norepinephrine
5 transporters;
- 506) peripheral benzodiazepam binding receptors — nucleoside
transporter proteins;
- 507) peripheral benzodiazepam binding receptors — peripheral
benzodiazepam binding receptors;
- 10 508) peripheral benzodiazepam binding receptors — sigma receptors;
- 509) peripheral benzodiazepam binding receptors — somatostatin
receptors;
- 510) peripheral benzodiazepam binding receptors — stromelysin 3;
- 511) peripheral benzodiazepam binding receptors — trypsin;
- 15 512) peripheral benzodiazepam binding receptors — MMP 1;
- 513) peripheral benzodiazepam binding receptors — MMP 2;
- 514) peripheral benzodiazepam binding receptors — MMP 3;
- 515) peripheral benzodiazepam binding receptors — MMP 7;
- 516) peripheral benzodiazepam binding receptors — MMP 9;
- 20 517) peripheral benzodiazepam binding receptors — membrane type
matrix metalloproteinase I;
- 518) peripheral benzodiazepam binding receptors — MMP 12;
- 519) peripheral benzodiazepam binding receptors — MMP 13;
- 520) peripheral benzodiazepam binding receptors — a tumor antigen;
- 25 521) folate binding receptors — a cathepsin type protease;

- 522) folate binding receptors — cathepsin D;
- 523) folate binding receptors — to cathepsin K;
- 524) folate binding receptors — cathepsin L;
- 525) folate binding receptors — cathepsin O;
- 5 526) folate binding receptors — fibroblast activation protein;
- 527) folate binding receptors — folate binding receptors;
- 528) folate binding receptors — matrilysin;
- 529) folate binding receptors — melanocyte stimulating hormone
receptor;
- 10 530) folate binding receptors — nitrobenzylthioinosine-binding receptors
or (nucleoside transporter);
- 531) folate binding receptors — norepinephrine transporters;
- 532) folate binding receptors — nucleoside transporter proteins;
- 533) folate binding receptors — sigma receptors;
- 15 534) folate binding receptors — somatostatin receptors;
- 535) folate binding receptors — stromelysin 3;
- 536) folate binding receptors — trypsin;
- 537) folate binding receptors — MMP 1;
- 538) folate binding receptors — MMP 2;
- 20 539) folate binding receptors — MMP 3;
- 540) folate binding receptors — MMP 7;
- 541) folate binding receptors — MMP 9;
- 542) folate binding receptors — membrane type matrix
metalloproteinase I;
- 25 543) folate binding receptors — MMP 12;

- 544) folate binding receptors — MMP 13;
- 545) folate binding receptors — a tumor antigen;
- 546) folate binding receptors — a cathepsin type protease;
- 547) folate binding receptors — cathepsin D;
- 5 548) folate binding receptors — to cathepsin K;
- 549) folate binding receptors — cathepsin L;
- 550) folate binding receptors — cathepsin O;
- 551) folate binding receptors — fibroblast activation protein;
- 552) folate binding receptors — folate binding receptors;
- 10 553) folate binding receptors — matipase;
- 554) folate binding receptors — melanocyte stimulating hormone
receptor;
- 555) folate binding receptors — nitrobenzylthioinosine-binding receptors
or (nucleoside transporter);
- 15 556) folate binding receptors — norepinephrine transporters;
- 557) folate binding receptors — nucleoside transporter proteins;
- 558) folate binding receptors — sigma receptors;
- 559) folate binding receptors — somatostatin receptors;
- 560) folate binding receptors — stromelysin 3;
- 20 561) folate binding receptors — trypsin;
- 562) folate binding receptors — MMP 1;
- 563) folate binding receptors — MMP 2;
- 564) folate binding receptors — MMP 3;
- 565) folate binding receptors — MMP 7;
- 25 566) folate binding receptors — MMP 9;

- 567) folate binding receptors — membrane type matrix metalloproteinase I;
- 568) folate binding receptors — MMP 12;
- 569) folate binding receptors — MMP 13;
- 5 570) folate binding receptors — a tumor antigen;
- 571) nucleoside transporter proteins — a cathepsin type protease;
- 572) nucleoside transporter proteins — cathepsin D;
- 573) nucleoside transporter proteins — to cathepsin K;
- 574) nucleoside transporter proteins — cathepsin L;
- 10 575) nucleoside transporter proteins — cathepsin O;
- 576) nucleoside transporter proteins — fibroblast activation protein;
- 577) nucleoside transporter proteins — nucleoside transporter proteins;
- 578) nucleoside transporter proteins — matrilysin;
- 579) nucleoside transporter proteins — melanocyte stimulating hormone receptor;
- 15 580) nucleoside transporter proteins — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 581) nucleoside transporter proteins — norepinephrine transporters;
- 582) nucleoside transporter proteins — nucleoside transporter proteins;
- 20 583) nucleoside transporter proteins — sigma receptors;
- 584) nucleoside transporter proteins — somatostatin receptors;
- 585) nucleoside transporter proteins — stromelysin 3;
- 586) nucleoside transporter proteins — trypsin;
- 587) nucleoside transporter proteins — MMP 1;
- 25 588) nucleoside transporter proteins — MMP 2;

- 589) nucleoside transporter proteins — MMP 3;
- 590) nucleoside transporter proteins — MMP 7;
- 591) nucleoside transporter proteins — MMP 9;
- 592) nucleoside transporter proteins — membrane type matrix
5 metalloproteinase I;
- 593) nucleoside transporter proteins — MMP 12;
- 594) nucleoside transporter proteins — MMP 13;
- 595) nucleoside transporter proteins — a tumor antigen;
- 596) melanocyte stimulating hormone receptor — a cathepsin type
10 protease;
- 597) melanocyte stimulating hormone receptor — cathepsin D;
- 598) melanocyte stimulating hormone receptor — to cathepsin K;
- 599) melanocyte stimulating hormone receptor — cathepsin L;
- 600) melanocyte stimulating hormone receptor — cathepsin O;
- 15 601) melanocyte stimulating hormone receptor — fibroblast activation
protein;
- 602) melanocyte stimulating hormone receptor — melanocyte
stimulating hormone receptor;
- 603) melanocyte stimulating hormone receptor — melanocyte
20 stimulating hormone receptor;
- 604) melanocyte stimulating hormone receptor —
nitrobenzylthioinosine-binding receptors or (nucleoside
transporter);
- 605) melanocyte stimulating hormone receptor — norepinephrine
25 transporters;

- 606) melanocyte stimulating hormone receptor — nucleoside transporter proteins;
- 607) melanocyte stimulating hormone receptor — sigma receptors;
- 608) melanocyte stimulating hormone receptor — somatostatin receptors;
- 5 609) melanocyte stimulating hormone receptor — stromelysin 3;
- 610) melanocyte stimulating hormone receptor — trypsin;
- 611) melanocyte stimulating hormone receptor — MMP 1;
- 612) melanocyte stimulating hormone receptor — MMP 2;
- 10 613) melanocyte stimulating hormone receptor — MMP 3;
- 614) melanocyte stimulating hormone receptor — MMP 7;
- 615) melanocyte stimulating hormone receptor — MMP 9;
- 616) melanocyte stimulating hormone receptor — membrane type matrix metalloproteinase I;
- 15 617) melanocyte stimulating hormone receptor — MMP 12;
- 618) melanocyte stimulating hormone receptor — MMP 13;
- 619) melanocyte stimulating hormone receptor — a tumor antigen;
- 620) sigma receptors — a cathepsin type protease;
- 621) sigma receptors — cathepsin D;
- 20 622) sigma receptors — to cathepsin K;
- 623) sigma receptors — cathepsin L;
- 624) sigma receptors — cathepsin O;
- 625) sigma receptors — fibroblast activation protein;
- 626) sigma receptors — sigma receptors;
- 25 627) sigma receptors — matrilysin;

- 628) sigma receptors — norepinephrine transporters;
- 629) sigma receptors — sigma receptors;
- 630) sigma receptors — somatostatin receptors;
- 631) sigma receptors — stromelysin 3;
- 5 632) sigma receptors — trypsin;
- 633) sigma receptors — MMP 1;
- 634) sigma receptors — MMP 2;
- 635) sigma receptors — MMP 3;
- 636) sigma receptors — MMP 7;
- 10 637) sigma receptors — MMP 9;
- 638) sigma receptors — membrane type matrix metalloproteinase I;
- 639) sigma receptors — MMP 12;
- 640) sigma receptors — MMP 13;
- 641) sigma receptors — a tumor antigen;
- 15 642) somatostatin receptors — a cathepsin type protease;
- 643) somatostatin receptors — cathepsin D;
- 644) somatostatin receptors — to cathepsin K;
- 645) somatostatin receptors — cathepsin L;
- 646) somatostatin receptors — cathepsin O;
- 20 647) somatostatin receptors — fibroblast activation protein;
- 648) somatostatin receptors — somatostatin receptors;
- 649) somatostatin receptors — matipase;
- 650) somatostatin receptors — melanocyte stimulating hormone
receptor;
- 25 651) somatostatin receptors — sigma receptors;

- 652) somatostatin receptors — somatostatin receptors;
- 653) somatostatin receptors — stromelysin 3;
- 654) somatostatin receptors — trypsin;
- 655) somatostatin receptors — MMP 1;
- 5 656) somatostatin receptors — MMP 2;
- 657) somatostatin receptors — MMP 3;
- 658) somatostatin receptors — MMP 7;
- 659) somatostatin receptors — MMP 9;
- 660) somatostatin receptors — membrane type matrix
- 10 metalloproteinase I;
- 661) somatostatin receptors — MMP 12;
- 662) somatostatin receptors — MMP 13;
- 663) somatostatin receptors — a tumor antigen ;
- 664) stromelysin 3 — a cathepsin type protease;
- 15 665) stromelysin 3 — cathepsin D;
- 666) stromelysin 3 — to cathepsin K;
- 667) stromelysin 3 — cathepsin L;
- 668) stromelysin 3 — cathepsin O;
- 669) stromelysin 3 — fibroblast activation protein;
- 20 670) stromelysin 3 — stromelysin 3;
- 671) stromelysin 3 — matipase;
- 672) stromelysin 3 — melanocyte stimulating hormone receptor;
- 673) stromelysin 3 — somatostatin receptors;
- 674) stromelysin 3 — trypsin;
- 25 675) stromelysin 3 — MMP 1;

- 676) stromelysin 3 — MMP 2;
- 677) stromelysin 3 — MMP 3;
- 678) stromelysin 3 — MMP 7;
- 679) stromelysin 3 — MMP 9;
- 5 680) stromelysin 3 — membrane type matrix metalloproteinase I;
- 681) stromelysin 3 — MMP 12;
- 682) stromelysin 3 — MMP 13;
- 683) stromelysin 3 — a tumor antigen;
- 684) trypsin — a cathepsin type protease;
- 10 685) trypsin — cathepsin D;
- 686) trypsin — to cathepsin K;
- 687) trypsin — cathepsin L;
- 688) trypsin — cathepsin O;
- 689) trypsin — fibroblast activation protein;
- 15 690) trypsin — trypsin;
- 691) trypsin — matipase;
- 692) trypsin — melanocyte stimulating hormone receptor;
- 693) trypsin — stromelysin 3;
- 694) trypsin — MMP 1;
- 20 695) trypsin — MMP 2;
- 696) trypsin — MMP 3;
- 697) trypsin — MMP 7;
- 698) trypsin — MMP 9;
- 699) trypsin — membrane type matrix metalloproteinase I;
- 25 700) trypsin — MMP 12;

- 701) trypsin — MMP 13;
- 702) trypsin — a tumor antigen;
- 703) MMP 1 — a cathepsin type protease;
- 704) MMP 1 — cathepsin D;
- 5 705) MMP 1 — to cathepsin K;
- 706) MMP 1 — cathepsin L;
- 707) MMP 1 — cathepsin O;
- 708) MMP 1 — fibroblast activation protein;
- 709) MMP 1 — matipase;
- 10 710) MMP 1 — melanocyte stimulating hormone receptor;
- 711) MMP 1 — stromelysin 3;
- 712) MMP 1 — MMP 1;
- 713) MMP 1 — MMP 2;
- 714) MMP 1 — MMP 3;
- 15 715) MMP 1 — MMP 7;
- 716) MMP 1 — MMP 9;
- 717) MMP 1 — membrane type matrix metalloproteinase I;
- 718) MMP 1 — MMP 12;
- 719) MMP 1 — MMP 13;
- 20 720) MMP 1 — a tumor antigen;
- 721) MMP-2 — a cathepsin type protease;
- 722) MMP-2 — cathepsin D;
- 723) MMP-2 — to cathepsin K;
- 724) MMP-2 — cathepsin L;
- 25 725) MMP-2 — cathepsin O;

- 726) MMP-2 — fibroblast activation protein;
- 727) MMP-2 — matripase;
- 728) MMP-2 — melanocyte stimulating hormone receptor;
- 729) MMP-2 — stromelysin 3;
- 5 730) MMP-2 — MMP 2;
- 731) MMP-2 — MMP 3;
- 732) MMP-2 — MMP 7;
- 733) MMP-2 — MMP 9;
- 734) MMP-2 — membrane type matrix metalloproteinase I;
- 10 735) MMP-2 — MMP-2;
- 736) MMP-2 — MMP-3;
- 737) MMP-2 — a tumor antigen;
- 738) MMP-3 — a cathepsin type protease;
- 739) MMP-3 — cathepsin D;
- 15 740) MMP-3 — to cathepsin K;
- 741) MMP-3 — cathepsin L;
- 742) MMP-3 — cathepsin O;
- 743) MMP-3 — matripase;
- 744) MMP-3 — MMP 3;
- 20 745) MMP-3 — MMP 7;
- 746) MMP-3 — MMP 9;
- 747) MMP-3 — membrane type matrix metalloproteinase I;
- 748) MMP-3 — MMP-3;
- 749) MMP-3 — a tumor antigen;
- 25 750) MMP 7 — a cathepsin type protease;

- 751) MMP 7 — cathepsin D;
- 752) MMP 7 — to cathepsin K;
- 753) MMP 7 — cathepsin L;
- 754) MMP 7 — cathepsin O;
- 5 755) MMP 7 — fibroblast activation protein;
- 756) MMP 7 — matipase;
- 757) MMP 7 — stromelysin 3;
- 758) MMP 7 — MMP 7;
- 759) MMP 7 — MMP 9;
- 10 760) MMP 7 — membrane type matrix metalloproteinase I;
- 761) MMP 7 — a tumor antigen;
- 762) MMP 9 — a cathepsin type protease;
- 763) MMP 9 — cathepsin D;
- 764) MMP 9 — to cathepsin K;
- 15 765) MMP 9 — cathepsin L;
- 766) MMP 9 — cathepsin O;
- 767) MMP 9 — matipase;
- 768) MMP 9 — MMP 9;
- 769) MMP 9 — membrane type matrix metalloproteinase I;
- 20 770) MMP 9 — a tumor antigen;
- 771) MMP 12 — a cathepsin type protease;
- 772) MMP 12 — cathepsin D;
- 773) MMP 12 — to cathepsin K;
- 774) MMP 12 — cathepsin L;
- 25 775) MMP 12 — cathepsin O;

- 776) MMP 12 — matipase;
- 777) MMP 12 — MMP 2;
- 778) MMP 12 — membrane type matrix metalloproteinase I;
- 779) MMP 12 — a tumor antigen;
- 5 780) MMP 13 — a cathepsin type protease;
- 781) MMP 13 — cathepsin D;
- 782) MMP 13 — to cathepsin K;
- 783) MMP 13 — cathepsin L;
- 784) MMP 13 — cathepsin O;
- 10 785) MMP 13 — matipase;
- 786) MMP 13 — membrane type matrix metalloproteinase I;
- 787) MMP 13 — a tumor antigen;
- 788) Membrane type matrix metalloproteinase — a cathepsin type protease;
- 15 789) Membrane type matrix metalloproteinase — cathepsin D;
- 790) Membrane type matrix metalloproteinase — to cathepsin K;
- 791) Membrane type matrix metalloproteinase — cathepsin L;
- 792) Membrane type matrix metalloproteinase — cathepsin O;
- 793) Membrane type matrix metalloproteinase — matipase;
- 20 794) Membrane type matrix metalloproteinase — membrane type matrix metalloproteinase I;
- 795) and Membrane type matrix metalloproteinase — a tumor antigen.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);
E1 is an inhibitor of thymidylate synthase and E2 is an inhibitor of nucleoside
transporter proteins.

- 5 In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);
E1 is an embodiment of 1E1.1, and E2 is an embodiment of 1E2.1.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);
E1 is an embodiment of 1E1.1, and E2 is an embodiment of 1E2.2.

10

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);
E1 is an embodiment of 1E1.1, and E2 is an embodiment of 1E2.3

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

- 15 E1 is an embodiment of 1E1.1, and E2 is an embodiment of 1E2.4.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);
E1 is an embodiment of 2E1.1, and E2 is an embodiment of 2E2.1.

- 20 In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);
E1 is an embodiment of 2E1.1, and E2 is an embodiment of 2E2.2..

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);
E1 is an embodiment of 2E1.1, and E2 is an embodiment of 2E2.3.

25

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 3E1.1, and E2 is an embodiment of 3E2.1.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

5 E1 is an embodiment of 3E1.2, and E2 is an embodiment of 3E2.1.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 3E1.2, and E2 is an embodiment of 1E2.1.

10 In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 3E1.2, and E2 is an embodiment of 1E2.2.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 3E1.2, and E2 is an embodiment of 1E2.3.

15

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 3E1.2, and E2 is an embodiment of 1E2.4.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

20 E1 is an embodiment of 4E1.1, and E2 is an embodiment of 1E2.1

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 4E1.1, and E2 is an embodiment of 1E2.2

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 4E1.1, and E2 is an embodiment of 1E2.3.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

5 E1 is an embodiment of 4E1.1, and E2 is an embodiment of 1E2.4.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 5E1.1, and E2 is an embodiment of 1E2.1.

10 In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 5E1.1, and E2 is an embodiment of 1E2.2.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 5E1.1, and E2 is an embodiment of 1E2.3.

15

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 5E1.1, and E2 is an embodiment of 1E2.4.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

20 E1 is an embodiment of 6E1.1, and E2 is an embodiment of 1E2.1.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 6E1.1, and E2 is an embodiment of 1E2.2.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

E1 is an embodiment of 6E1.1, and E2 is an embodiment of 1E2.3.

In preferred embodiments of (embodiment "1STLP #.X", for X=1, 2, 3,... 795);

5 E1 is an embodiment of 6E1.1, and E2 is an embodiment of 1E2.4.

In a preferred embodiment ET is an anti-cancer drug comprised of at least one tumor-selective targeting ligand a masked effector agent that can stimulate the innate immune system and that can be unmasked at the tumor.

10

In a preferred embodiment ET is an anti-cancer drug comprised of at least one tumor-selective targeting ligand one or more masked effector agents that can stimulate the innate immune system wherein that effector agent when unmasked comprises a :

- 15 1.) N-formyl peptide receptor agonists
2.) Tuftsin receptor agonists
3.) Lipoxin A(4) receptor agonists
4.) Leukotriene B4 agonists
5.) 3-formyl-1-butyl-pyrophosphates receptor agonists
20 6.) Gal alpha(1,3)Gal. analogs

In a preferred embodiment of the above embodiment, ET is also comprised of a second group which can irreversibly modify a biomolecule that is over-expressed at the tumor. In a preferred embodiment ET is also comprised of two targeting ligands of (embodiments TLP #.X, wherein X=1, 2, 3,... 795).

25

A preferred embodiment of the present invention comprises a compound with a masked intracellular transport ligand.

A preferred embodiment of the present invention is a method of targeting an immune response against a tumor which is comprised of the following steps:

- 1.) Sensitizing the patient against a set of neoantigens, and
- 2.) Administering, to the patient, a compound that interacts with tumor components and thereby generates the neoantigens in the tumor.

A preferred embodiment, of the above method is comprised of administering to the patient a compound ET, wherein ET is comprised of a targeting ligand that binds to a targeting receptor present at increased amounts at the tumor and an effector agent E that irreversibly chemically modifies a biomolecule that is increased at the tumor. Numerous examples of suitable compounds ET for this purpose are given in this document. In preferred embodiments of the above, the neoantigens are derived from one or more of the following:

- 1.) Prostate specific Antigen
- 2.) Human glandular kallikrein 2
- 3.) Prostatic acid phosphatase
- 4.) Plasmin
- 5.) Placental type alkaline phosphatase
- 6.) Matriptase
- 7.) Matrix metalloproteinases
- 8.) Thymidine phosphorylase
- 9.) Trypsin
- 10.) Urokinase
- 11.) Fatty Acid Synthase
- 12.) Steroid sulfatase
- 13.) Epidermal growth factor receptor
- 14.) Mitogen activated protein kinase kinase
- 15.) Phosphatidylinositol 3-kinase
- 16.) Mitogen activated protein kinase
- 17.) Thymidylate synthase

- 18.) Protein kinase A
- 19.) Fibroblast activation protein/ seprase
- 20.) P-glycoprotein

5 A preferred embodiment of the present invention is a method for generating neoantigens (AG) from a target receptor (m) by contacting the target receptor with a compound E-T in which E includes the structure: RN-L-V, wherein RN is a group that binds with high affinity to the target m, L is a linker, and V is a group that can covalently modify the target m; and wherein RN and V are linked
10 together in a manner so as to allow RN to retain binding affinity to m and V to functionally modify m; and wherein T is a targeting agent. In a preferred embodiment V is a free radical generator and modifies m by the production of free radicals.

15 A preferred embodiment of the present invention is a method of generating neoantigens comprised of contacting a tumor with a compound ET which is comprised of a tumor-selective targeting ligand wherein E is an effector agent comprised of an irreversible enzyme inhibitor. In a preferred embodiment E is a mechanism based suicide inhibitor for a target enzyme and the neoantigens are
20 derived from said enzyme. In a preferred embodiment said enzyme is overexpressed at tumor cells. In a preferred embodiment E is a mechanism based suicide inhibitor for PSA. In a preferred embodiment E is a mechanism based suicide inhibitor or irreversible inhibitor for Prostate Specific Antigen, or Human glandular kallikrein 2, or Prostatic acid phosphatase, or Plasmin, , or
25 Matriptase, or A Matrix metalloproteinases, Trypsin, or Urokinase, or Fatty Acid Synthase, or Steroid sulfatase, or Epidermal growth factor receptors, or Mitogen

activated protein kinase kinase, or Phosphatidylinositol 3-kinase, or Mitogen
activated protein kinase, or an Estrogen receptor, or Thymidylate synthase, or
Protein kinase A, or Fibroblast activation protein or seprase, or P-glycoprotein,
or Ribonucleotide diphosphate reductase, or Dihydrofolate reductase, or Src
5 Kinases, or Platelet-derived growth factor receptors, or MMP 7, or MMP 1, or
MMP 2, or MMP 3, or MMP 9, or MMP 12, or MMP 13, or Membrane type MMP
1, or A Cathepsin, or Cathepsin B, or Glutathione S -Transferases.

10 A preferred embodiment of the present invention is a method of treating a
patient with prostate cancer which is comprised of the following steps:

- a. Sensitizing the patient against a set of neoantigens derived from PSA
- b. Administering, to the patient, a compound that interacts with PSA and
generates said PSA derived neoantigens at the tumor

15 In a preferred embodiment of the above method, PSA neoantigen generating
compound is an irreversible enzyme inhibitor of PSA. In an even more preferred
embodiment, the neoantigen generating inhibitor is comprised of an irreversible
inhibitor of PSA and a targeting ligand that binds to PSMA, or Urokinase, or
sigma receptors, or plasmin, or a matrix metalloproteinase.

20 A preferred embodiment of the present invention is a method of to treat A
patient with prostate cancer comprised of the following steps:

- a) Sensitizing the patient against a set of neoantigens derived from multiple
tumor-associated proteins that are enriched at prostate cancer cells; and
- b) Administering, to the patient, a set of compounds that irreversibly modify

25 said tumor-associated proteins thereby generating neoantigens;

In a preferred embodiment the set of administered compounds that generate the
neoantigens irreversibly modify PSA and one or more of the proteins from the

following list: Human glandular kallikrein 2, and Prostatic acid phosphatase, Plasmin, Urokinase, Fatty Acid Synthase, Epidermal growth factor receptors, Mitogen activated protein kinase kinase; Phosphatidylinositol 3-kinase, Thymidylate synthase, or Protein kinase A, or Fibroblast activation protein or
5 seprase, or P-glycoprotein, or Ribonucleotide diphosphate reductase, or Dihydrofolate reductase, or Src Kinases, or Platelet-derived growth factor receptors, or MMP 7, or MMP 1, or MMP 2, or MMP 3, or MMP 9, or MMP 12, or MMP 13, or Membrane type MMP 1, or a Cathepsin, or Cathepsin B, or PSMA;
In a preferred embodiment of the above, the neoantigen generating compounds
10 are also comprised of one or more targeting ligands for one or more receptor that are increased at prostate tumor cells.

A preferred embodiment of the present invention is a method to treat a patient with breast cancer, or a patient with other forms of cancer, that have over-
15 expression of the epidermal growth factor receptor, or related proteins which is comprised of:

- a) Sensitizing the patient against a set of neoantigens derived from said epidermal growth factor receptor
- b) Administering, to the patient, a compound that interacts with the epidermal
20 growth factor receptor and generates said neoantigens at the tumor.

In a preferred embodiment the neoantigen generating compound is comprised of at least one targeting ligand that binds to a receptor that is increased on breast cancer cells. In a preferred embodiment, the neoantigen generating compound
ET is comprised of two different tumor-selective targeting ligands. In a preferred
25 embodiment, the effector group that irreversibly chemically modifies the

epidermal growth factor receptor is a structure of embodiment Eneo 31, Eneo32, Eneo33, Eneo34, Eneo35...or Eneo42.

5 Methods of Drug Synthesis

The drugs of the present class can be prepared by a variety of synthetic approaches well known to one skilled in the arts. In order to effectively treat cancer, multiple targeted drugs can be required. Accordingly, a modular approach is preferred in which a small number of basic components such as

10 linkers, triggers, and masked intracellular transporter ligands are synthesized and coupled with the desired targeting ligands and effector groups. A large variety of methods can be utilized to couple the respective components. The general steps include chemical protection of interfering groups, coupling, and deprotection. A preferred type of coupling reaction is the formation of an amide

15 or ester bond. General references are given below and synthetic methodologies illustrated by examples that follow. The following references relate to this subject matter: Bodanszky M.; Bodanszky A. (1994) "The Practice of Peptide Synthesis" Springer-Verlag, Berlin Heidelberg; Greene, Theodora W.; Wuts, Peter G.M. (1991) "Protective Groups in Organic Synthesis", John Wiley & Sons,

20 Inc.; March, Jerry (1985) "Advanced Organic Chemistry", John Wiley & Sons Inc., the contents of which are incorporated herein by reference in their entirety.

The content of all references cited within this document are hereby incorporated by reference in entirety.

Equivalents

Those skilled in the arts can recognize or be able to ascertain, using no more than routine experimentation, many equivalents to the inventions, materials, methods, and components described herein. Such equivalents are intended to

5 be within the scope of the claims of this patent.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing

10 from the scope of the invention encompassed by the appended claims.

EXAMPLES:

The following examples serve to illustrate certain aspects of the present invention. One skilled in the arts will recognize many other examples that are within the scope of the present invention. One skilled in the arts will recognize

- 5 many instances where alternate reagents, protecting groups, or reaction sequences may be employed to prepare compounds encompassed by the present invention. The length of the various linker groups employed in the following examples can readily be changed by appropriate substitutions without altering the chemistry.

10

General Comments

In the following examples, the terms "coupled" or "coupling" are used to refer to the formation of an ester or amide bond from an alcohol or amine and acid. A large number of agents and methods are well known to one skilled in the arts for

15 the coupling of amine or alcohols to acids. Relevant coupling agents and methods may be found within the following reference relates to this subject matter: Bodanszky M.; Bodanszky A. (1994) "The Practice of Peptide Synthesis" Springer-Verlag, Berlin Heidelberg; Trost, Barry; (1991) Comprehensive Organic Synthesis, Pergamon Press, the contents of which are incorporated herein by

20 reference in their entirety.

- Unless otherwise specified, all reactions described in the examples can be conducted in an inert solvent under an inert atmosphere 4. All compounds and intermediates, unless indicated, can be purified by routine methods such as
- 25 chromatography, distillation, or crystallization and stored in a stable form.

In compounds with chiral centers, the R, S, and racemic mixtures are to be considered within the scope of the present invention unless otherwise specified or unless specified in the references that relate to the starting materials or components.

5

Some of the nomenclature employed in the following examples was generated by the software CS Chemdraw 5.0, CambridgeSoft Corporation.

10

Abbreviations :

Bsm - (1,1-Dioxo-1H-1 λ 6-benzo[b]thiophen-2-yl)-methyl

Bsmoc - (1,1-Dioxo-1H-1 λ 6-benzo[b]thiophen-2-yl)-methoxy-carbonyl

Fm- (9H-Fluoren-9-yl)-methyl

15 Fmoc- (9H-Fluoren-9-yl)-methoxy-carbonyl

TDBS- Tert-butyldimethylsilyl

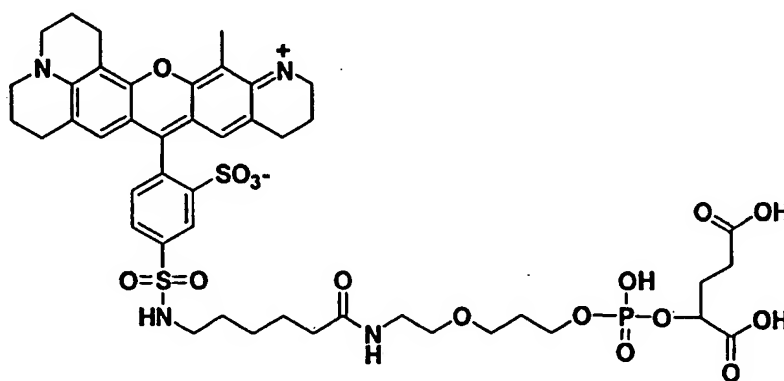
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Example 1.1, 1.2

Prostatic adenocarcinoma cells have high concentrations of the enzyme
Glutamate carboxypeptidase II or Prostatic Specific Membrane Antigen (PSMA)
on the cell surface. PSMA is a zinc carboxypeptidase, which catalyzes the
5 hydrolysis of N-acetyl-aspartylglutamate and gamma glutamates. The enzyme is
potently inhibited by phosphorous based transition state analogs. 2-
(phosphonomethyl)-pentanedioic acid inhibits the enzyme with a K_i of 0.3
nanomolar. The following references relate to this subject matter: US Patent
5,804,602 9/8/98 Slusher, et al., "Methods of Cancer Treatment Using
10 NAALADase Inhibitors"; US Patent 5,795,877 8/18/98 Jackson, et al.,
"Inhibitors of NAALADase Enzyme Activity"; Jackson PF, et al., "Design,
Synthesis, and Biological Activity of a Potent Inhibitor of the Neuropeptidase N-
Acetylated Alpha-Linked Acidic Dipeptidase," *J Med Chem*, 39(2):619-22 (1996),
the contents of which are incorporated herein by reference in their entirety.

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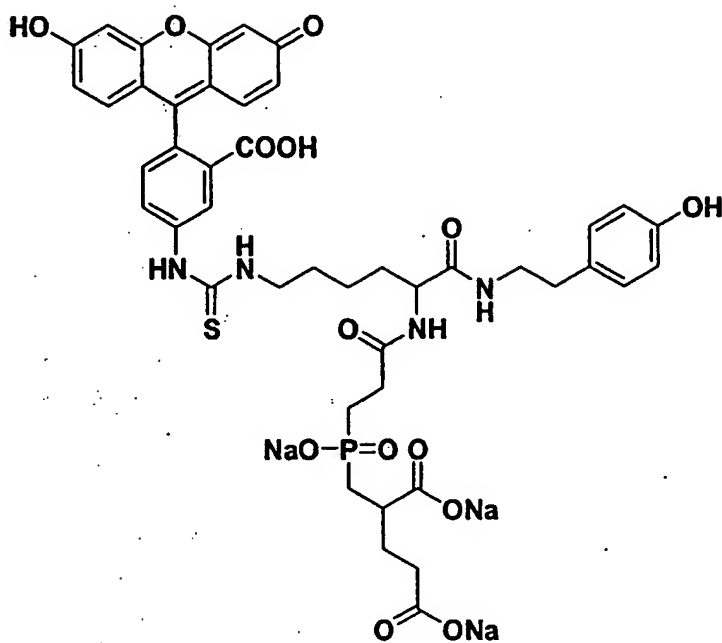
Compound 1 was synthesized and found to potently inhibit PSMA with a K_i of 20
nanomolar. Structure 1 has the fluorescent dye, Texas red, coupled by a linker



to a moiety that tightly binds to the active site of PSMA.

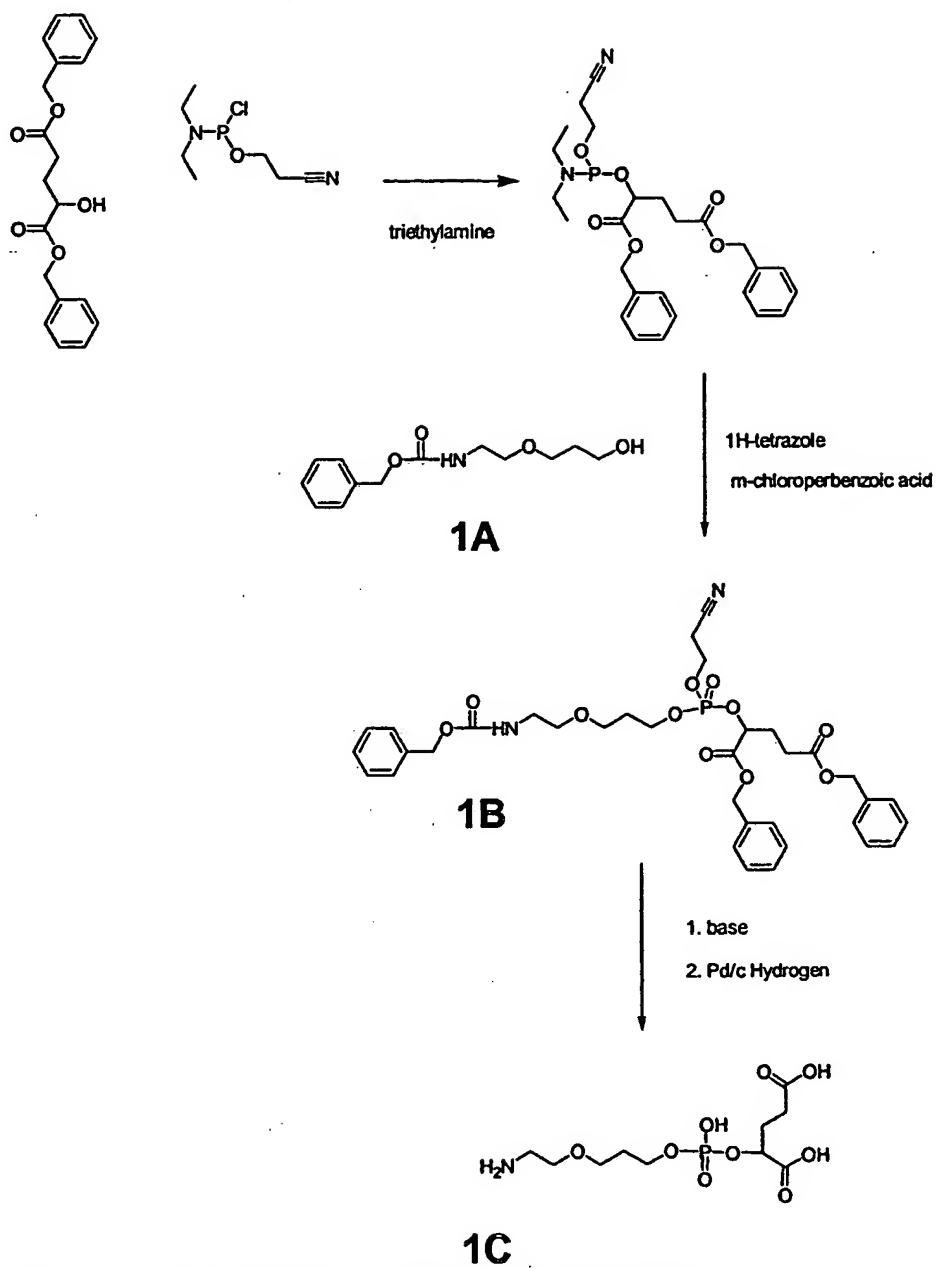
Compound 1

Compound 1.1 was also synthesized and found to inhibit PSMA with a K_i of 3.4 nanomolar.

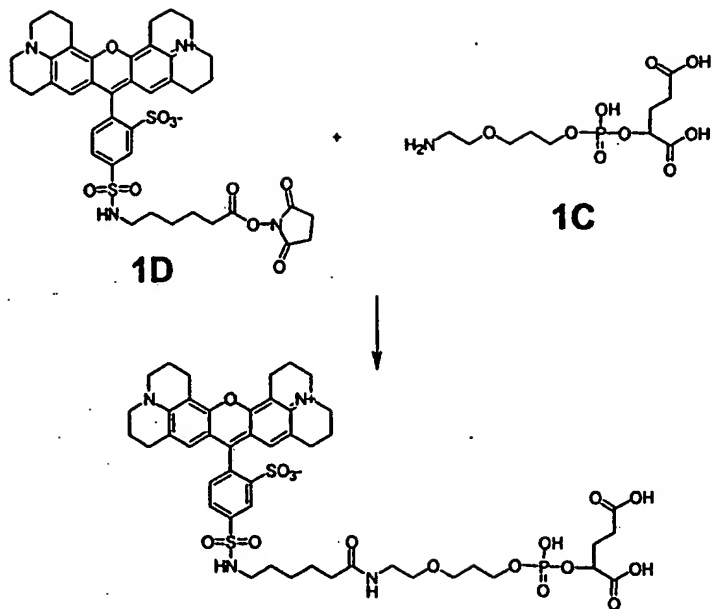


5

Compound 1.1



Compound 1 was synthesized by the scheme shown below:



Compound 1

The Synthesis of Compound 1

- Dibenzyl 2-hydroxyglutarate (5mM) in 10 ml tetrahydrofuran and 5 mM of
- 5 triethylamine was reacted at -78°C with 2-cyanoethyl N,N diisopropyl chlorophosphoramidite. After 1 hour 5.3 mM of 1A was added along with 5.3 mM of 1H tetrazole in 2 ml dimethylformamide. The reaction was allowed to warm to room temperature. After 2 hours it was cooled again to -78°C and 5.5 mM of m-Cl-perbenzoic acid in 5 ml dimethylformamide was added. After 20
- 10 minutes the reaction was allowed to warm to room temperature. Compound 1B was then purified by silica gel chromatography using a gradient from 100% chloroform to 50:1 chloroform methanol. Yield was 74%. NMR was consistent with the structure 1B.
- 15 Compound 1B 135 mg was dissolved in 5 ml of acetonitrile and 2.4 ml of triethylamine was added. After 24 hours the solvent was evaporated and the

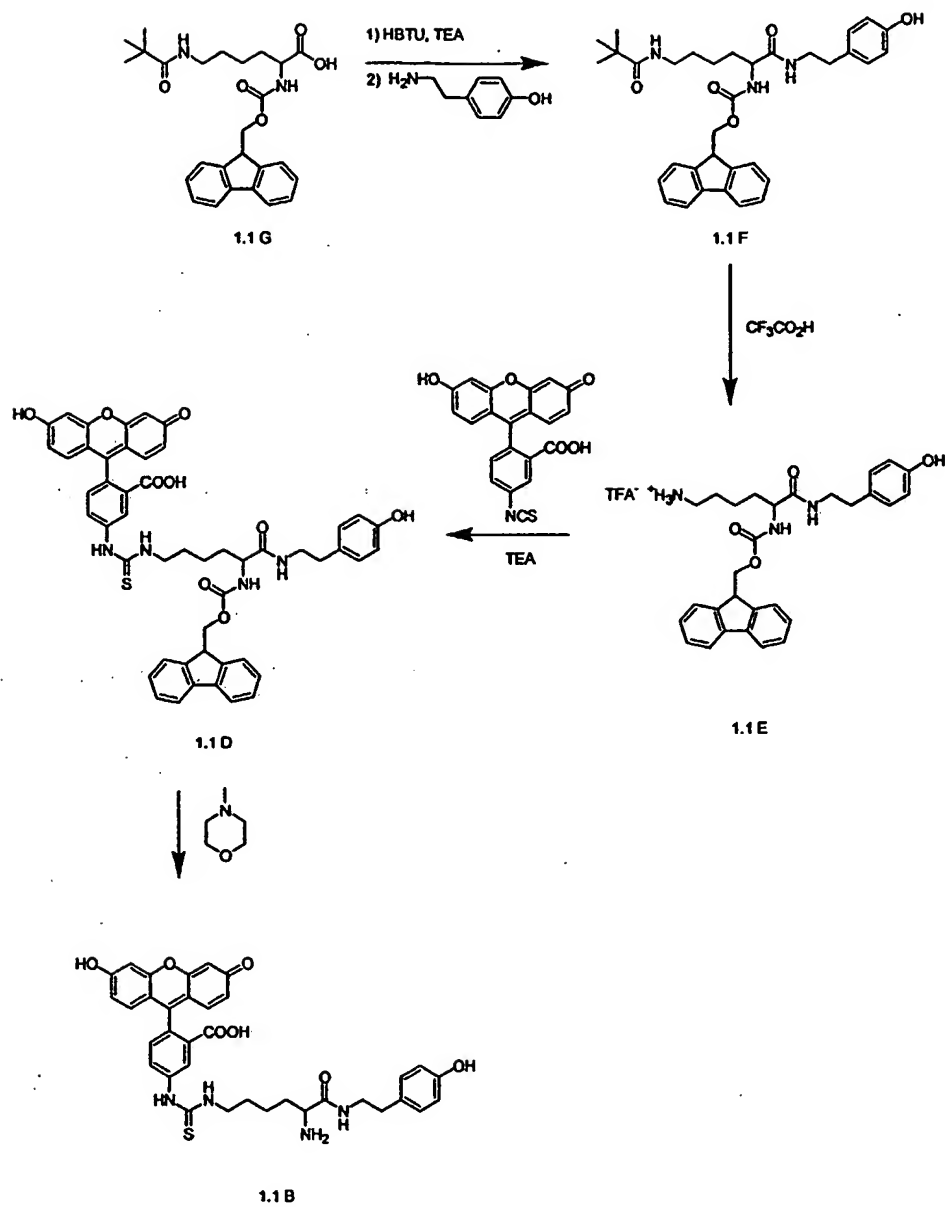
residue dissolved. 4 ml methanol and 12 mg of 10% Pd on carbon was added.

The suspension was then treated with hydrogen at atmospheric pressure for 4 hours, filtered and evaporated to yield 108 mg of 1C. Proton and phosphorous NMR were consistent with structure 1C.

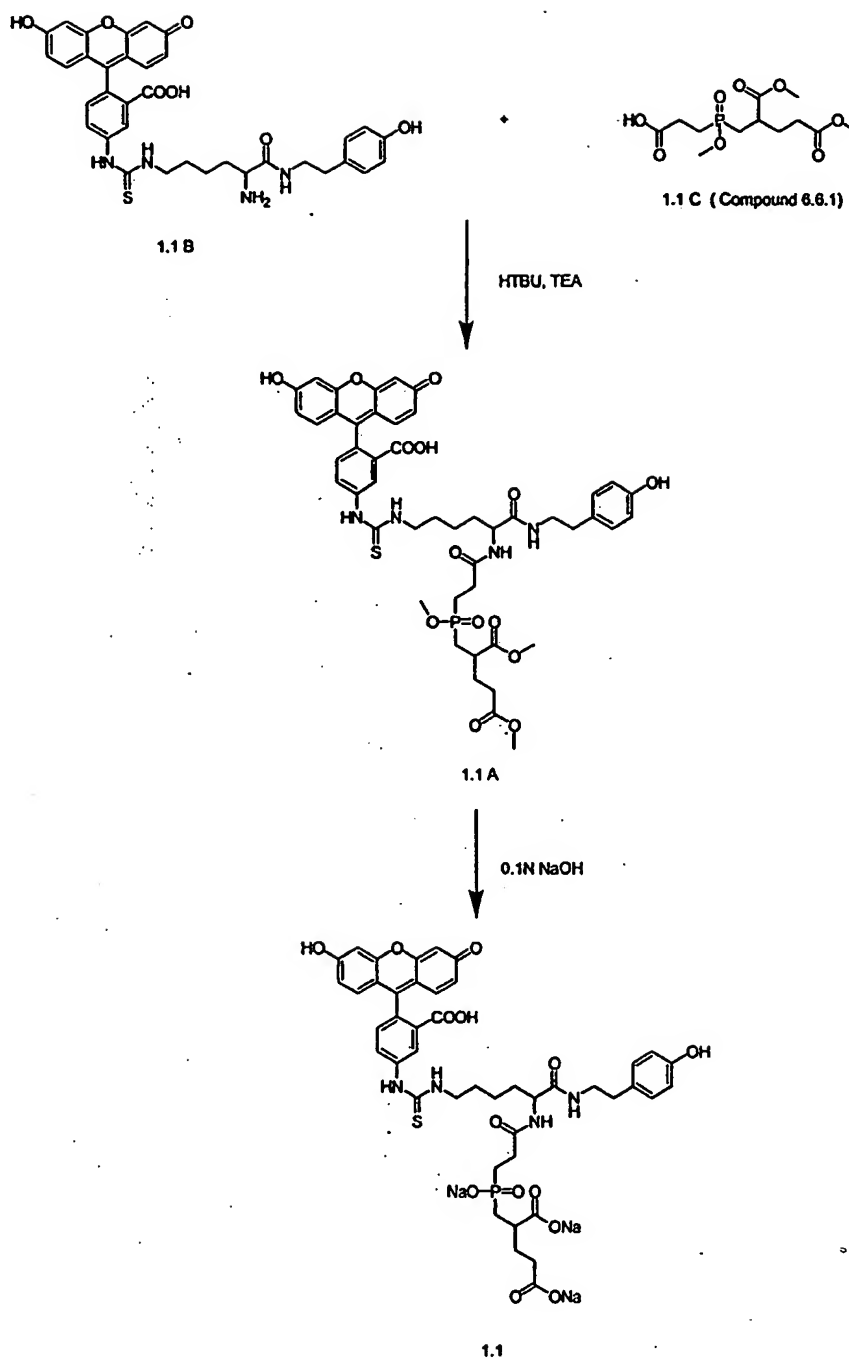
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Compound 1 was synthesized by the reaction of the tributylammonium salt of 1C (10 micromoles) and 3 micromoles of 1D (Molecular Probes) in 150 microliters of dimethylformamide and 10 microliters of tributylamine at room temperature for 12 hours. Compound 1 was then purified by preparative reverse phase HPLC using
10 a C18 column and elution with a gradient from 0 to 70% acetonitrile in 20 mM ammonium bicarbonate buffer. The structure of compound 1 was confirmed by proton phosphorous and 2 dimensional proton NMR.

Compound 1.1 was synthesized according to Schemes 1-2.



Scheme 1



Scheme 2

N^α-Fmoc-N^ε-Boc-L-lysine (10 mmol) in DMF (20 mL) was activated with HBTU
 (O-(1H-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate)

and triethylamine (10 mmol of each) for 5 min., and condensed with 10 mmol of 4-(2-aminoethyl)phenol for 6 hours at r.t.(room temperature). The reaction mixture was evaporated under vacuum, dissolved in ethylacetate, washed with 0.5 M citric acid, water, 5% NaHCO₃, water, brine, and evaporated under vacuum. Flash chromatography on silicagel (chloroform/methanol 50:1) afforded 7.0 mmol, (70% yield) of compound 1.1F, which was characterized by ¹H NMR.

Compound 1.1F (1 mmol) was dissolved in a 50% solution of trifluoroacetic acid in chloroform. The solution, after 1 hour at r.t., was evaporated under vacuum, re-evaporated from toluene, and dried under vacuum to give compound 1.1E as a glassy residue (¹H NMR). This residue was dissolved in chloroform (3 mL) and treated with a solution of fluorescein-5-isothiocyanate (1 mmol) in 1 mL DMF and 0.3 mL triethylamine. After 3 hours at r.t., the mixture was evaporated under vacuum. Flash chromatography of the residue (gradient from 10% to 20% methanol in methylene chloride) afforded 0.63 mmol (yield, 63%) of compound 1.1D, the structure of which was confirmed by ¹H and COSY NMR.

Compound 1.1D (0.114 mmol) was dissolved in a mixture of 250 microliters of DMF and 250 microliters of N-methylmorpholine. The solution was kept tightly closed for 24 hours at 45° C, and then evaporated under vacuum. The residue was extracted two times with hexane and dried under vacuum to give quantitative yield of compound 1.1B.

(Compound 1.1C is the same as compound 6.6.1, the synthesis of which is described at a later point).

Compound 1.1C (0.144 mmol) was activated with HBTU and N-methylmorpholine (0.158 mmol of each) in 0.350 mL of DMF for 5 min. at r.t. and the resulting solution was added to the solution of compound 1.1B (0.114 mmol) in 0.300 mL of DMF. After 24 hours at r.t., the reaction mixture was evaporated under vacuum and compound 1.1A was isolated by flash chromatography on silicagel (gradient from chloroform/methanol 10:1 to chloroform/methanol/water 50:10:1) in 51% yield. The product was characterized by ^1H , COSY, and ^{31}P NMR.

- 10 Compound 1.1A (27 micromols) was de-blocked to compound 1.1 by treatment with methanol / 0.1 N NaOH 1:1 for 2.5 hours. Compound 1.1 was isolated by preparative reverse phase HPLC (20% acetonitrile in 20 mM ammonium bicarbonate buffer pH 7.8) in 52% yield as the ammonium salt. The structure was confirmed by ^1H , COSY, and ^{31}P NMR.

15

Inhibition of PSMA by Compounds 1 and 1.1

- PSMA was prepared from LNCaP prostatic carcinoma cells as described by Pinto J.T. et al., *Clinical Cancer Res.* Vol.2 p.1445 (1996). The enzyme was assayed employing radiolabelled N-acetylasparylglutamate as a substrate and monitoring the generation of glutamic acid in the presence of varying concentrations of Compound 1 or 1.1. The data demonstrated that Compound 1 inhibited the enzyme 50% at a concentration of 20 nM. Compound 1.1 inhibited the enzyme 50% at 3.4 nM.

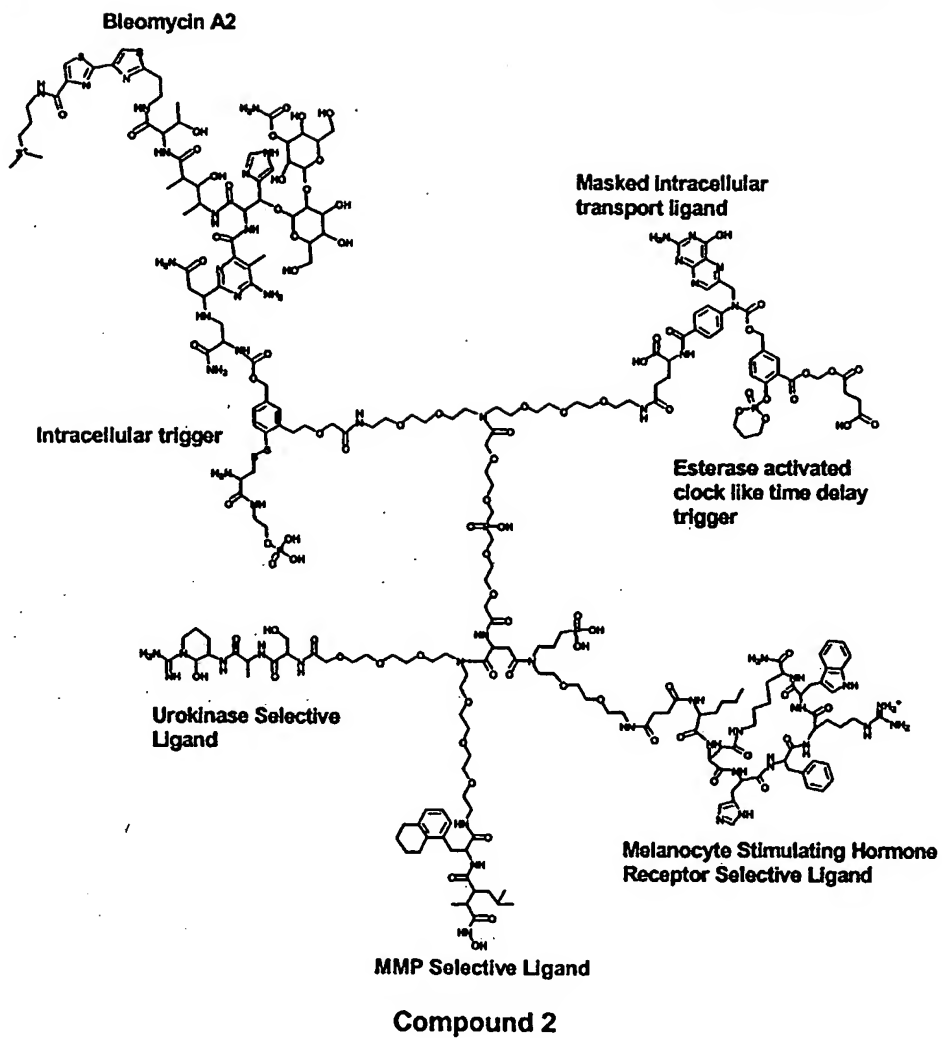
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Example 2

Compound 2 is a multifunctional drug delivery vehicle with targeting ligands for urokinase, matrix metalloproteinases (1,2,3,9, and MT-MMP-1) and melanocyte stimulating hormone receptor. The drug has a masked folic acid group as an

5 intracellular transport ligand that will be activated by esterase. Bleomycin A2 will be freed upon cleavage of a disulfide trigger by thiol reductases. Five hundred molecules of bleomycin delivered intracellularly are sufficient to kill a cell. The drug is expected to have activity against malignant melanoma. The following references relate to this subject matter: Pron G., et al., "Internalisation of the

10 Bleomycin Molecules Responsible for Bleomycin Toxicity: A Receptor-mediated Endocytosis Mechanism," *Biochemical Pharmacology*, 57:45-56 (1999), the contents of which are incorporated herein by reference in their entirety.



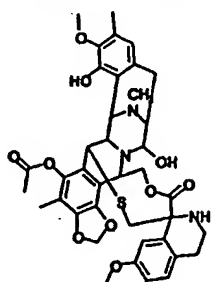
Compound 2 may be prepared by the methods similar to those described for compound 24 by replacing compound 23.2.a with bleomycin A2.

Example 3

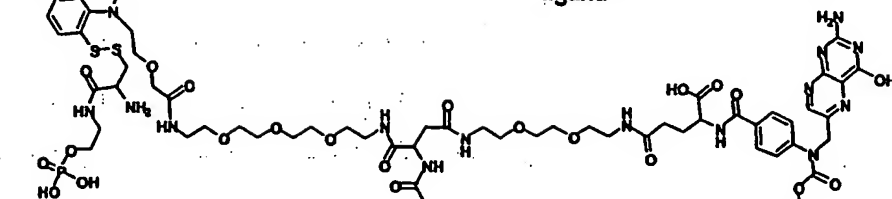
Compound 3 is a multifunctional drug delivery vehicle that will be selective for prostatic cancer cells that bear both the laminin receptor and PSMA. The drug has a masked folic acid moiety, as an intracellular transport with a clock like time
5 delayed trigger that will be activated by esterase. The toxin Ecteinasidin 743 will be liberated following activation of the intracellular trigger by intracellular glutathione or by thioreductases. Ecteinasidin 743 is cytotoxic at picomolar concentrations. The following references relate to this subject matter: Zewail-Foote M.; Hurley L.H., "Ecteinasidin 743: A Minor Groove Alkylator that Bends
10 DNA toward the Major Groove," *J Med Chem*, 42(14):2493-2497 (1999); Takebayashi Y., et al., "Poisoning of Human DNA Topoisomerase I by Ecteinasidin 743, an Anticancer Drug that Selectively Alkylates DNA in the Minor Groove," *Proc Natl Acad Sci USA*, 96:7196-7201 (1999); Hendriks H.R., et al., "High Antitumour Activity of ET743 against Human Tumour Xenografts from
15 Melanoma, Non-Small-Cell Lung and Ovarian Cancer." *Ann Oncol*, 10(10):1233-40 (1999), the contents of which are incorporated herein by reference in their entirety.

Compound 3 may be prepared by the methods described for compound 6 by
20 replacing compound 6.2.0c with compound 3.1. Compound 3.1 may be prepared by reacting Ecteinasidin 743 with compound 3.2 in an inert solvent in the presence of a base such as pyridine and then selectively cleaving the Bsm ester with tris(2-aminoethyl)amine. Compound 3.2 may be prepared by treating compound 38.3 with phosgene in an inert solvent.

Ecteinascidin

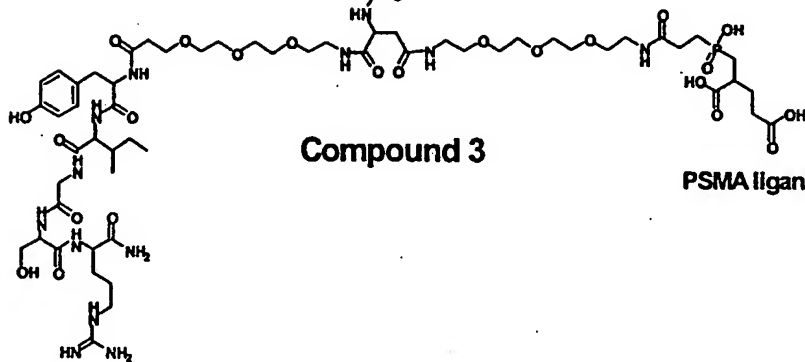


Masked intracellular transport ligand



Intracellular Trigger

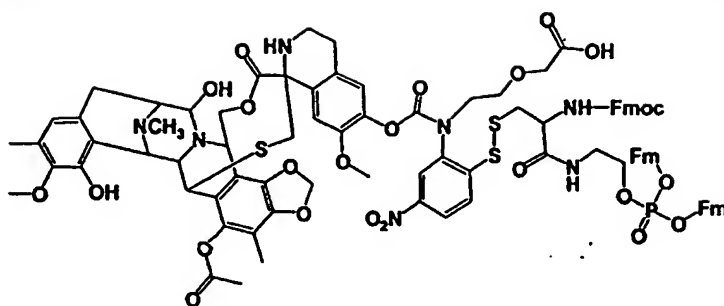
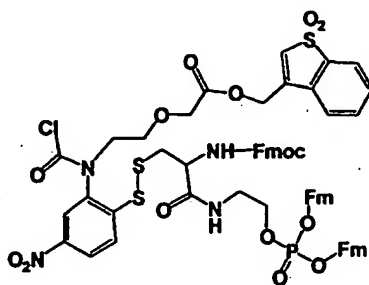
Esterase activated clock like time delay trigger



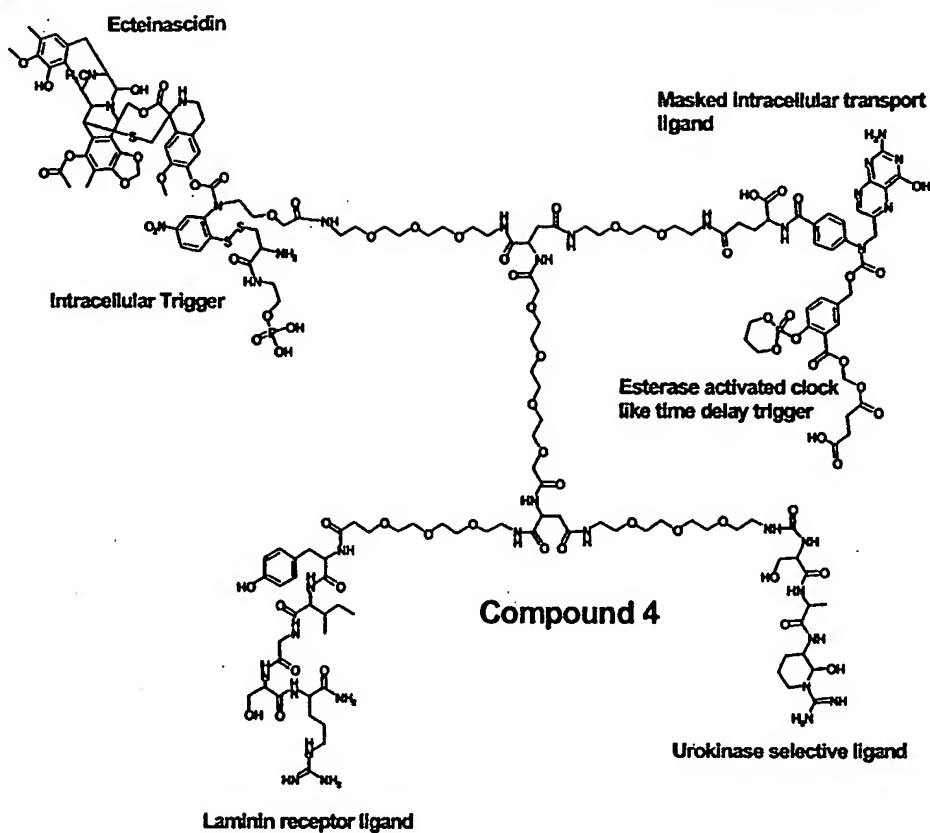
Compound 3

PSMA ligand

Laminin receptor ligand

**Compound 3.1****Compound 3.2****Example 4**

- 5 Compound 4 is a multifunctional drug delivery vehicle with targeting ligands for urokinase and laminin receptors. Like compound 3, the drug will liberate Ecteinascidin 743 following activation of the intracellular trigger by glutathione or by thioreductases.
- 10 Compound 4 may be prepared by the methods described for compound 11 by replacing compound 6.2.0c with compound 3.1.



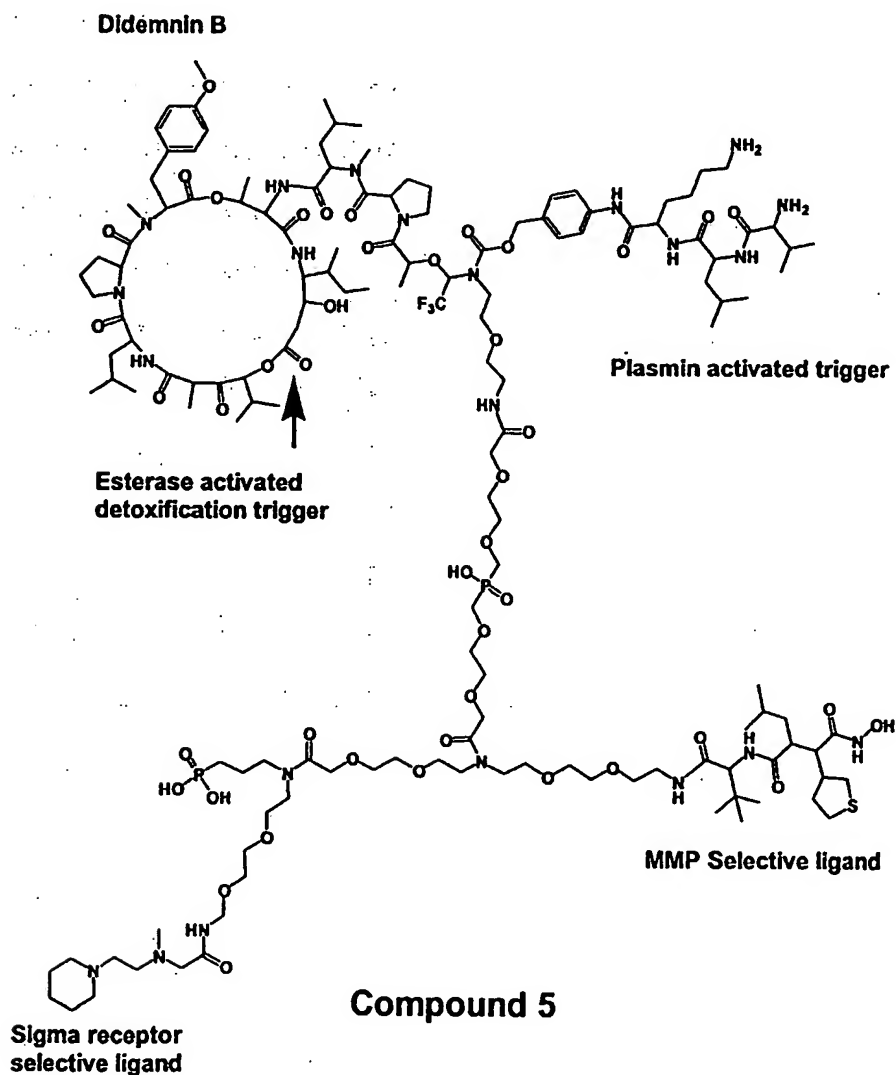
Example 5

- 5 Compound 5 is a multifunctional drug delivery vehicle with targeting ligands for sigma receptors and MMP7, MMP2, MMP1, and MMP3. Didemnin B will be released upon activation of a trigger by plasmin. Didemnin B is cytotoxic at nanomolar to sub-nanomolar concentrations. However, Didemnin B has not proven clinically useful due to its poor antitumor selectivity and toxicity.
- 10 Compound 5 will bind essentially irreversibly to the surface cells that are jointly positive for sigma receptors and the targeted matrix metalloproteinases. Tumor associated plasmin will toxify the drug by liberating the Didemnin B. Ubiquitous nonspecific esterases will detoxify the drug by opening the cyclic ring of the

- toxin. The ratio between plasmin mediated toxification and esterase mediated detoxification will determine the cytotoxicity. The drug is expected to have selective toxicity for cells that are jointly positive for sigma receptors, the targeted MMP's, and plasmin. The following references relate to this subject matter: Kiss
- 5 I., et al., "Investigation on the Substrate Specificity of Human Plasmin using Tripeptidyl-P-Nitroanilide Substrates," *Biochem Biophys Res Comm*, 131(2):928-934 (1985); Sakai R., et al., "Structure-Activity Relationships of the Didemnins," *J Med Chem*, 39:2819-2834 (1996); Meng L., et al., "The Antiproliferative Agent Didemnin B Uncompetitively Inhibits Palmitoyl Protein Thioesterase,"
- 10 *Biochemistry*, 27:10488-10492 (1998); Ahuja D., et al., "Inhibition of Protein Synthesis by Didemnin B: How EF-1 α Mediates Inhibition of Translocation," *Biochemistry*, 39:4339-4346 (2000); Mittelman A., et al., "Phase II Clinical Trial of Didemnin B in Patients with Recurrent or Refractory Anaplastic Astrocytoma or Glioblastoma Multiforme (NSC 325319)," *Invest New Drugs*, 17(2):179-82
- 15 (1999); Jones D.V., et al., "Phase II Study of Didemnin B in Advanced Colorectal Cancer," *Invest New Drugs*, 10(3):211-3 (1992); Grubb D.R., et al., "Didemnin B Induces Cell Death by Apoptosis: The Fastest Induction of Apoptosis ever Described," *Biochem Biophys Res Commun*, 215(3):1130-6 (1995); Kucuk O., et al., "Phase II Trial of Didemnin B in Previously Treated Non-Hodgkin's
- 20 Lymphoma: An Eastern Cooperative Oncology Group (ECOG) Study," *Am J Clin Oncol*, 23(3):273-7 (2000); Sondak V.K., et al., "Didemnin B in Metastatic Malignant Melanoma: A Phase II Trial of the Southwest Oncology Group," *Anticancer Drugs*, 5(2):147-50 (1994); Williamson S.K., et al., "Phase II Evaluation of Didemnin B in Hormonally Refractory Metastatic Prostate Cancer. A Southwest Oncology Group Study," *Invest New Drugs*, 13(2):167-70 (1995);
- 25 Lobo C., et al., "Effect of Dehydrodidemnin B on Human Colon Carcinoma Cell

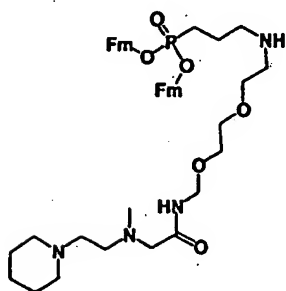
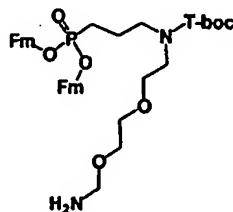
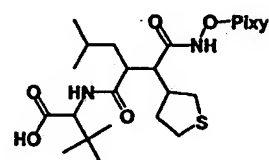
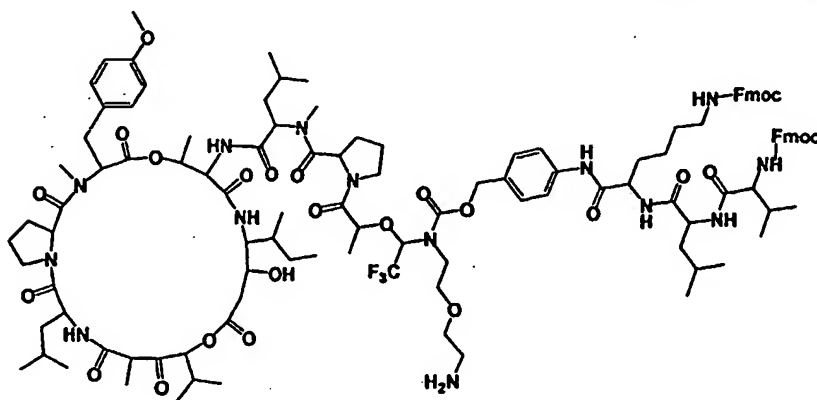
Lines," *Anticancer Res*, 17(1A):333-6 (1997); Geldof A.A., et al., "Cytotoxicity and Neurocytotoxicity of New Marine Anticancer Agents Evaluated using in Vitro Assays," *Cancer Chemother Pharmacol*, 44(4):312-8 (1999), the contents of which are incorporated herein by reference in their entirety.

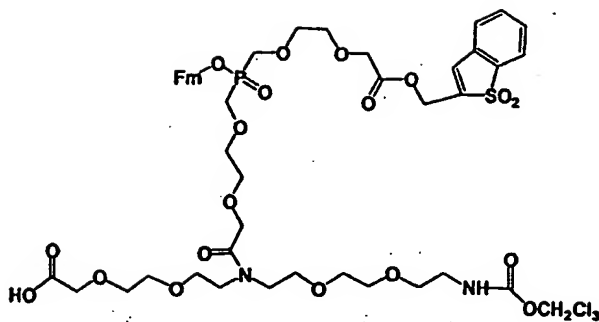
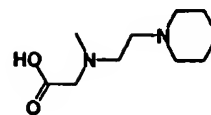
5



Compound 5 may be prepared by a multi-step process. Compound 5.1 may be coupled to compound 17.4b. The product may then be treated with Zn and acid to remove the trichloroethoxycarbonyl group. The product may then be coupled to compound 20.2.2a. The Bsm ester may then be selectively cleaved with

5 tris(2-aminoethyl)amine. The product may then be coupled with compound 5.2. Deprotection with acid to remove the pixyl group followed by treatment with base to remove the Fm and Fmoc groups will give compound 5.

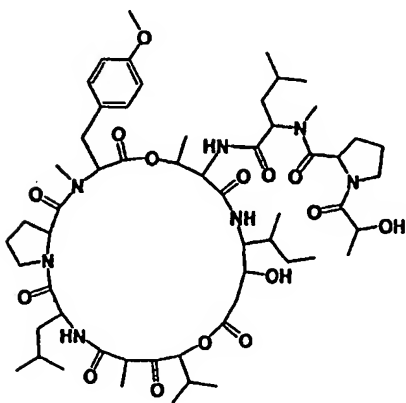
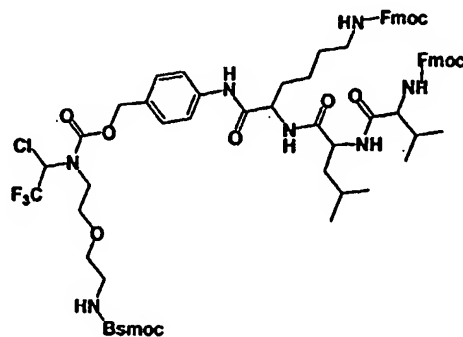
**Compound 5.1****Compound 5.3****Compound 20.2.2a****Compound 5.2**

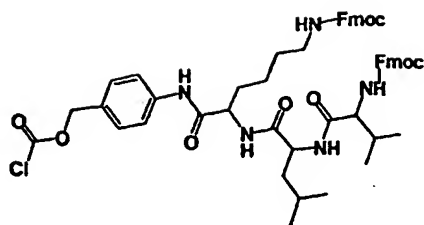
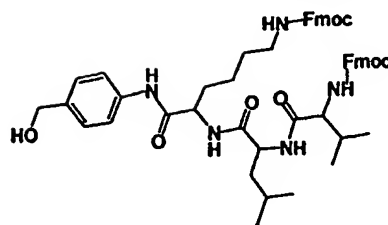
**Compound 17.4****Compound 14.5**

Compound 5.1 may be prepared by coupling compound 14.5 and compound 5.3 and then treating with acid to remove the T-Boc group. Compound 5.3 may be prepared by treating compound 13b3 with di-*t*-butyl pyrocarbonate in an inert solvent and then selectively removing the trityl group with acid.

Compound 5.2 may be prepared by reacting Didemnin B and compound 5.4 in an inert solvent in the presence of base and then selectively removing the Bsmoc group with tris(2-aminoethyl)amine.

10

**Didemnin B****Compound 5.4**

**Compound 5.5****Compound 5.6**

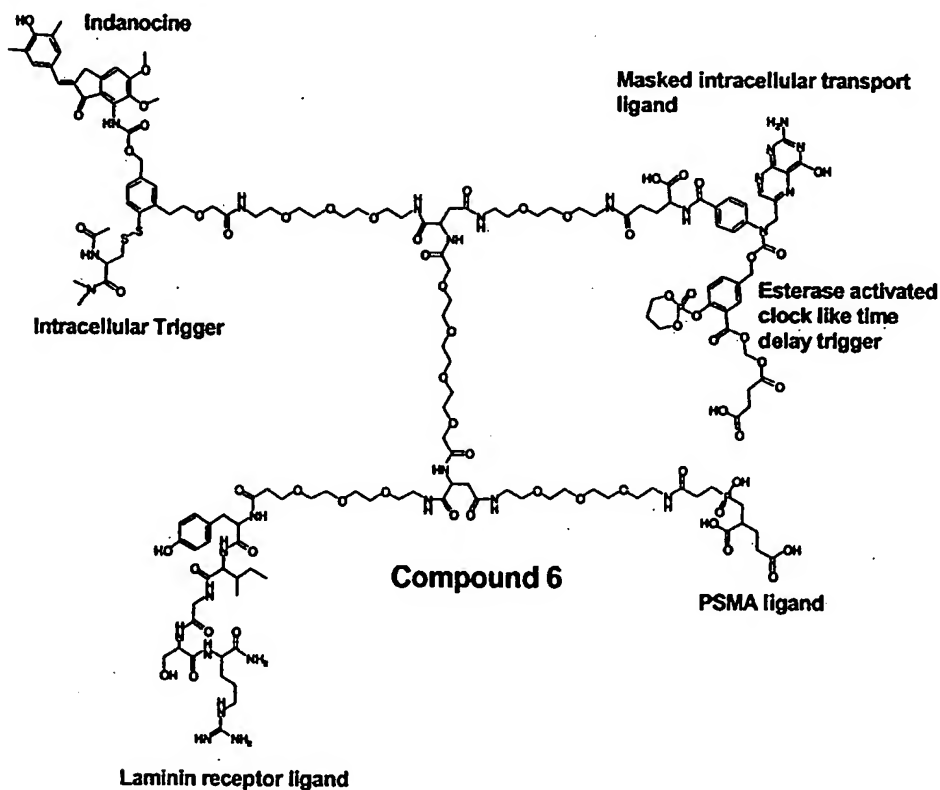
Compound 5.4 may be prepared by a multistep process. Compound 5.5 may be reacted with [2-(2-Amino-ethoxy)-ethyl]-carbamic acid 1,1-dioxo-1H-1λ6-

- 5 benzo[b]thiophen-2-ylmethyl ester in an inert solvent in the presence of a base such as pyridine. The product may then be treated with trifluoroacetaldehyde in an inert solvent and then treated with a reagent such as phosphorous trichloride to give compound 5.4
- 10 Compound 5.5 may be prepared by treating compound 5.6 with phosgene in an inert solvent. Compound 5.6 may be prepared by a multi-step process. The compounds p-aminobenzyl alcohol and L- N-α- allyloxycarbonyl- N ε-Fmoc-lysine may be coupled and then the product may be deblocked by with Pd(0). The product may then be coupled to L-N-allyloxycarbonyl leucine. Deblocking
- 15 with Pd(0) followed by coupling to D- Fmoc-valine will give compound 5.6.

Example 6

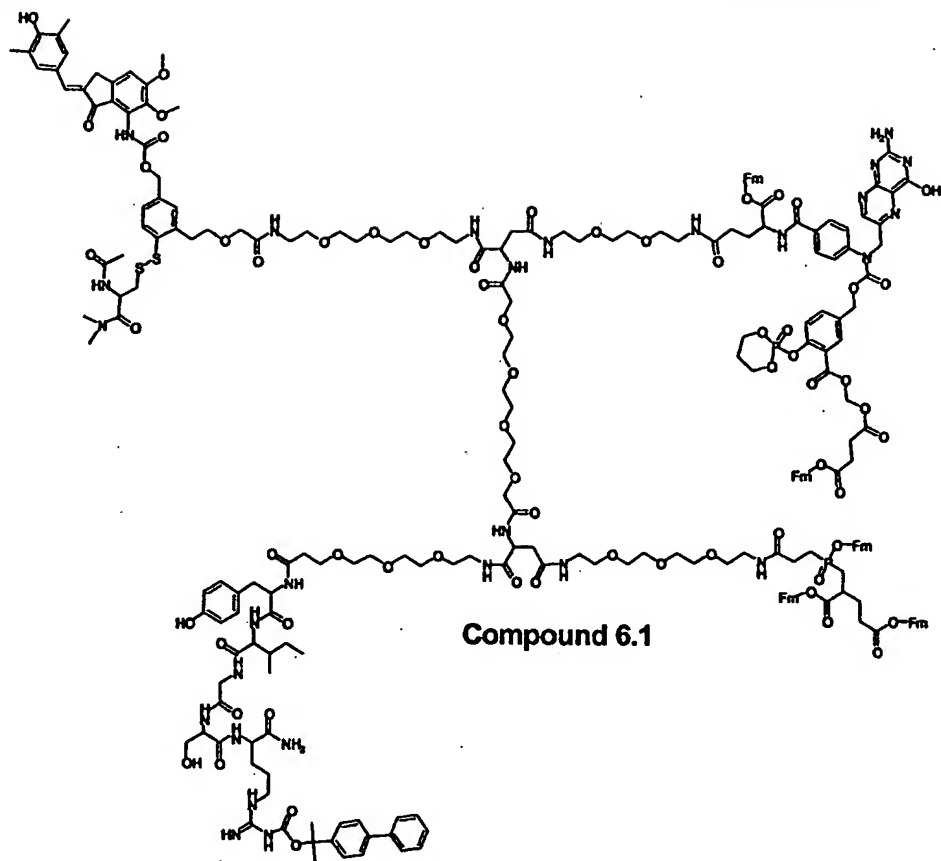
- Compound 6 is a multifunctional drug delivery vehicle that will be selective for
- 20 prostatic cancer cells that bear both the laminin receptor and PSMA. The drug has a masked folic acid moiety as an intracellular transport with a clock like time

- delayed trigger that will be activated by esterase. The toxin indanocine will be liberated following activation of the intracellular trigger by intracellular glutathione or by thio reductases. The affinity of the drug for PSMA +, laminin receptor + cells should be extremely high as each ligand independently will bind with Ki in the nanomolar range. The following references relate to this subject matter:
- 5 Leioni L., et al., "Indanocine, a Microtubule-Binding Indanone and a Selective Inducer of Apoptosis in Multidrug-Resistant Cancer Cells," *J Nat Cancer Inst*, 92(3):217-224 (2000), the contents of which are incorporated herein by reference in their entirety.

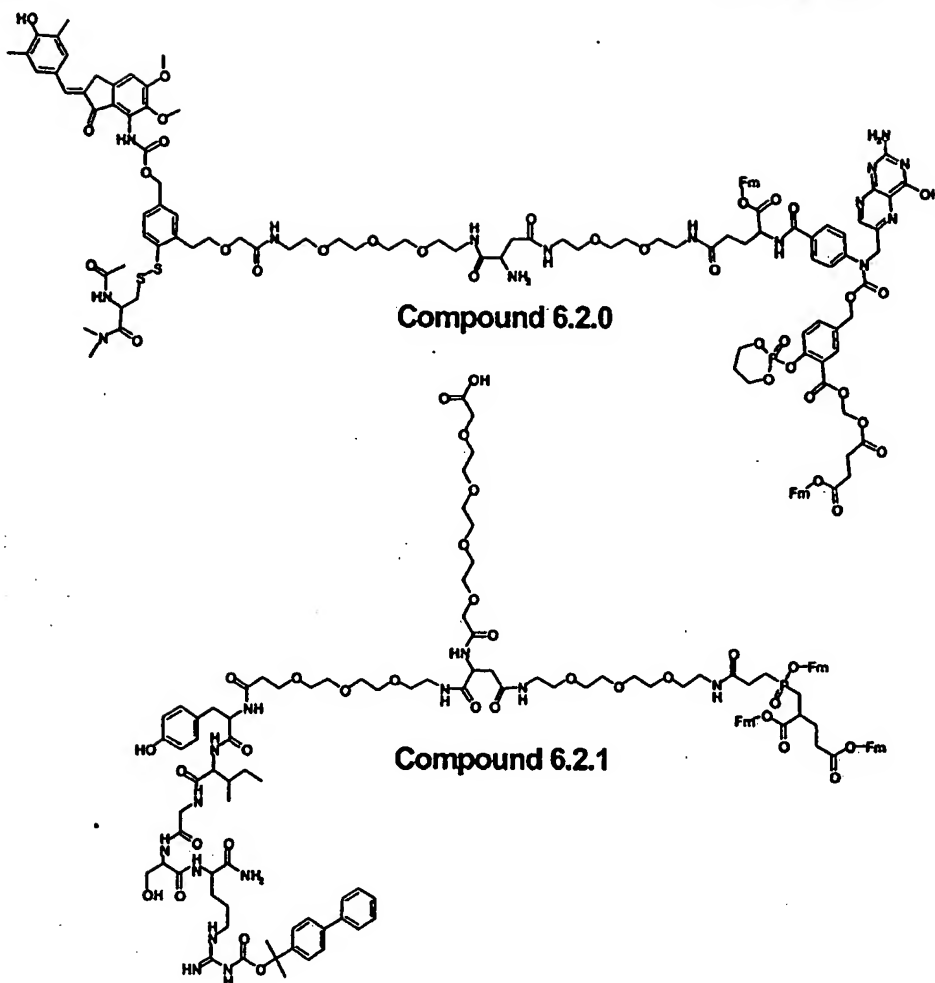


10

Compound 6 may be prepared by treating compound 6.1 with acid to remove the 2-Biphenyl-4-yl-propan-2-oxy-carbonyl protecting group and then treating with base to cleave the Fm esters.

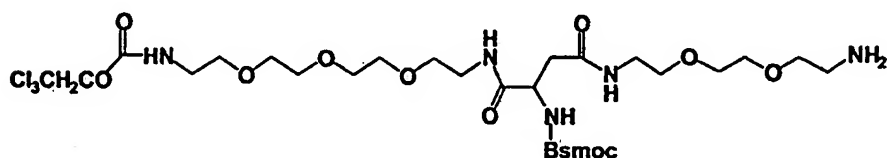
**Compound 6.1**

- Compound 6.1 may be synthesized by coupling compound 6.2.0 and compound
- 5 6.2.1. Standard peptide coupling reagents, such as dicyclohexylcarbodiimide or O-benzotriazol-1-yl-tetramethyluronium hexafluorophosphate, may be employed in an inert solvent with a base such as triethylamine.

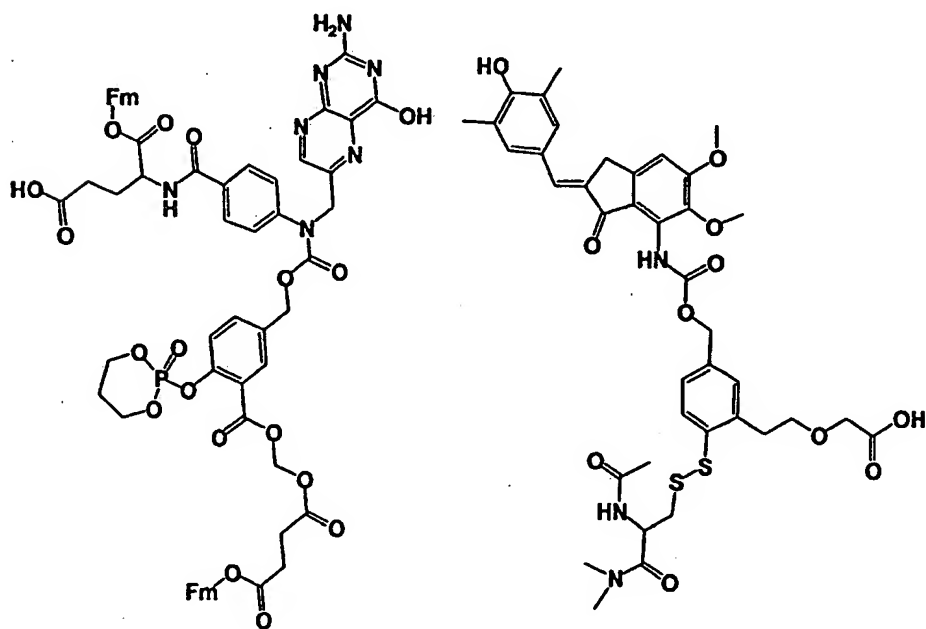


- Compound 6.2.0 may be prepared by a multi-step process. Compound 6.2.0a
- 5 and compound 6.2.0b may be coupled and then treated with Zn to remove the trichloroethoxycarbonyl group. The product may then be coupled with compound 6.2.0c. The Bsmoc group may then be selectively removed by treating with tris(2-aminoethyl)amine under conditions that will leave the Fmoc group intact to give compound 6.2.0. The following references relate to this subject matter:
- 10 Just G.; Grozinger K.; "A Selective, Mild Cleavage of Trichloroethyl Esters, Carbamates, and Carbonates to Carboxylic Acids, Amines, and Phenols using

Zinc/Tetrahydrofuran/pH 4.2-7.2 Buffer," *Synthesis*, 457-458 (1976); Carpino L.A., et al., "New Family of Base- and Nucleophile-Sensitive Amino-Protecting Groups. A Michael-Acceptor-Based Deblocking Process. Practical Utilization of the 1,1-Dioxobenzo[*b*]thiophene-2-ylmethyloxycarbonyl (Bsmoc) Group," *J Am Chem Soc*, 119:9915-9916 (1997); Carpino L.A., et al., "The 1,1-Dioxobenzo[*b*]thiophene-2-ylmethyloxycarbonyl (Bsmoc) Amino-Protecting Group," *J Org Chem*, 64:4324-4338 (1999), the contents of which are incorporated herein by reference in their entirety.

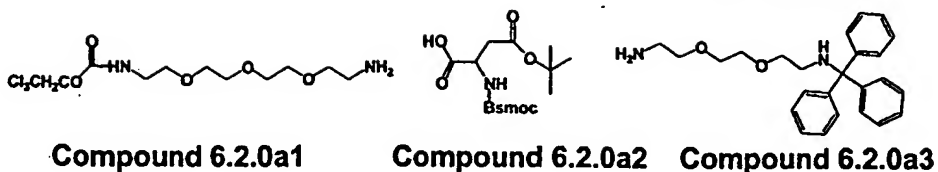


Compound 6.2.0a



Compound 6.2.0b

Compound 6.2.0c



Compound 6.2.0a may be prepared by a multi-step process. Compound 6.2.0a1
 5 may be coupled to compound 6.2.0a2. The product may then be treated with acid to cleave the t-butyl ester and then may be coupled to compound 6.2.0a3. Treatment with acid will then give compound 6.2.0a.

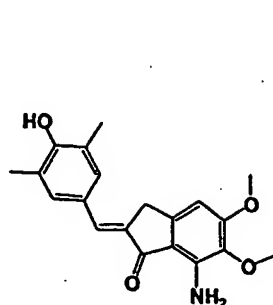
Compound 6.2.0a1 may be prepared by a multi-step process. Treating 2-[2-(2-
 10 (2-Amino-ethoxy)-ethoxy]-ethoxy]-ethylamine with one equivalent of trityl chloride and base and isolating the monotritylated product will give (2-[2-(2-(2-Amino-ethoxy)-ethoxy)-ethoxy]-ethyl)-trityl-amine. This may then be treated with 2,2,2 trichloroethyl chloroformate and base. Treatment with acid will then give compound 6.2.0a1.

15 Compound 6.2.0a2 may be prepared by treating L- aspartic acid β - t-butyl ester with (1,1-Dioxo-1H-1 λ 6-benzo[b]thiophen-2-yl)-methyl chloroformate and base in an inert solvent or under Schotten-Bauman conditions.

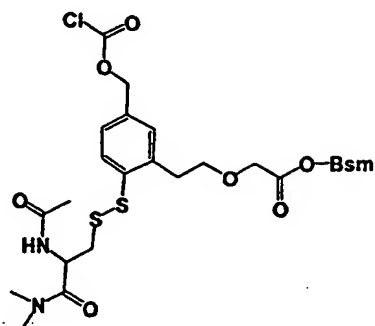
20 Compound 6.2.0.a3 may be prepared by treating 2-[2-(2-Amino-ethoxy)-ethoxy]-ethylamine with one equivalent of trityl chloride and base.

Compound 6.2.0c may be prepared by reacting indanocine and compound 6.2.0b1 in an inert solvent in the presence of a base such as pyridine and then

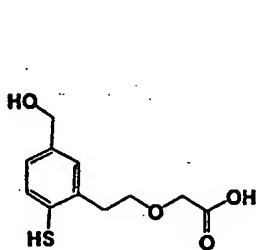
treating with with tris(2-aminoethyl)amine under conditions that will leave the Fm groups intact.



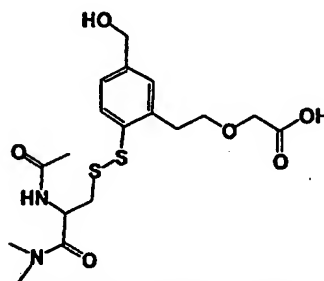
Indanocine



Compound 6.2.0b1



Compound 6.2.0b2

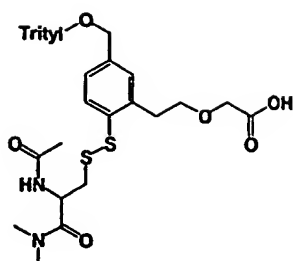


Compound 6.2.0b3

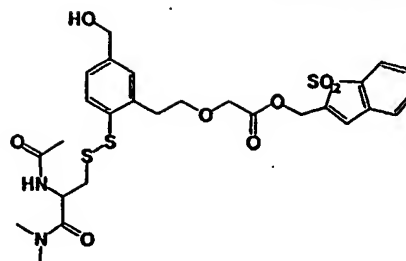
5

Compound 6.2.0b1 may be prepared by a multi-step process. Treating N-acetyl-L- cysteine N,N dimethylamide with diethyl azidocarboxylate, then reacting the product with compound 6.2.0b2, will give the mixed disulfide compound 6.2.0b3. Treatment with trityl chloride and base will give compound

10 6.2.0b4. Treatment with (1,1-Dioxo-1H-1λ6-benzo[b]thiophen-2-yl)-methanol and a reagent such as dicyclohexylcarbodiimide, followed by treatment with acid to remove the trityl group will give compound 6.2.0b5. Treatment with phosgene in an inert solvent will give compound 6.2.0b1.



Compound 6.2.0b4



Compound 6.2.0b5

The following references relate to this subject matter: Mukaiyama T.; Takahashi K., "A Convenient Method for the Preparation of Unsymmetrical Disulfides by the use of Diethyl Azodicarboxylate," *Tetrahedron Letters*, 56:5907-5908 (1968), the contents of which are incorporated herein by reference in their entirety.

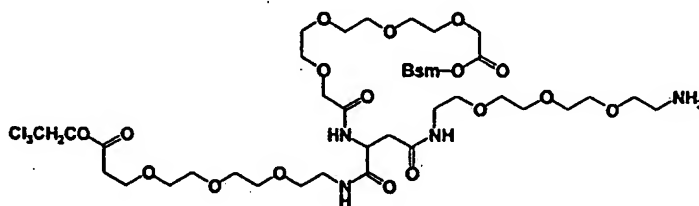
Alternatively, a variety of other methods may also be employed to form the mixed disulfide compound described above. The following references relate to this subject matter: Harpp D.N., et al., "A New Synthesis of Unsymmetrical Disulfides," *Tetrahedron Letters*, 41:3551-3554 (1970); Derbesy G.; Harpp D.N., "A Simple Method to Prepare Unsymmetrical Di- Tri- and Tetrasulfides," *Tetrahedron Letters*, 35(30):5381-5384 (1994); Harpp D.N.; Back T.G., "The Synthesis of Some New Cysteine-Containing Unsymmetrical Disulfides," *J Org Chem*, 36(24):3828-3829 (1971), the contents of which are incorporated herein by reference in their entirety.

Compound 6.2.0b2 may be prepared by a multi-step process. A Friedel-Crafts reaction between 4-mercapto-benzoic acid and chlorocarbonylmethoxy-acetic acid methyl ester will give 4-mercapto-3-(2-methoxycarbonylmethoxy-acetyl)-benzoic acid. Reduction of the resulting ketone with Zn/HCL will give 4-

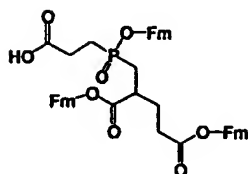
- mercapto-3-(2-methoxycarbonylmethoxy-ethyl)-benzoic acid. Treatment with borane in a solvent such as tetrahydrofuran will reduce the carboxylic acid to the alcohol and give [2-(5-Hydroxymethyl-2-mercapto-phenyl)-ethoxy]-acetic acid methyl ester. Hydrolysis of the methyl ester will give compound 6.2.0b2. The
- 5 following references relate to this subject matter: Gore P.H., "Aromatic Ketone Synthesis," in *Friedel-Crafts and Related Reactions*, Olah G.A. (edt.), John Wiley & Sons, p.55 (1964); Read R.R.; Wood J. Jr., "o-n-Heptylphenol," *Org Syn Coll Volume 3*, pp. 444-446; Yoon N.M.; Pak C.S., "Selective Reductions. XIX. The Rapid Reaction of Carboxylic Acids with Borane-Tetrahydrofuran. A Remarkable
- 10 Convenient Procedure for the Selective Conversion of Carboxylic Acids to the Corresponding Alcohols in the Presence of Other Functional Groups," *J Org Chem*, 33(16):2786-2792 (1973), the contents of which are incorporated herein by reference in their entirety.

Compound 6.2.0b may be described by methods detailed in example 32. (See

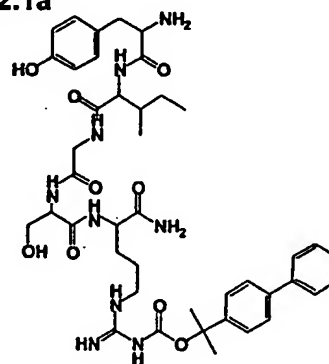
15 compound 32.1).



Compound 6.2.1a



Compound 6.2.1b



Compound 6.2.1c

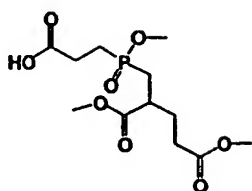
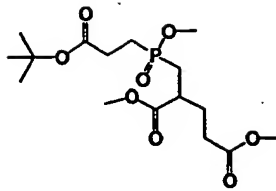
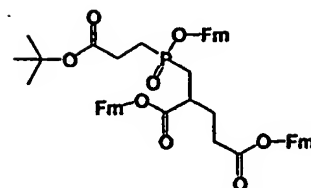
Compound 6.2.1 may be prepared by a multi-step process. Compound 6.2.1a and compound 6.2.1b may be coupled and the product treated with Zn to remove the trichloroethoxycarbonyl group. The product may then be coupled with compound 6.2.1c. Treatment with tris(2-aminoethyl)amine under conditions that will leave the Fm groups intact will then give compound 6.2.1.

Compound 6.2.1a may be prepared by a multi-step process. Compound 6.2.0a2 may be coupled to 3-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-propionic acid 2,2,2-trichloro-ethyl ester. The product may be treated with acid to cleave the t-butyl ester and then may be coupled to (2-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-ethyl)-trityl-amine. The product may then be treated with base to remove the Bsmoc group and coupled to (2-{2-[2-(1,1-Dioxo-1H-1λ6-benzo[b]thiophen-2-ylmethoxycarbonylmethoxy)-ethoxy]-ethoxy}-ethoxy)-acetic acid. Acid treatment will remove the trityl group and give compound 6.2.1a.

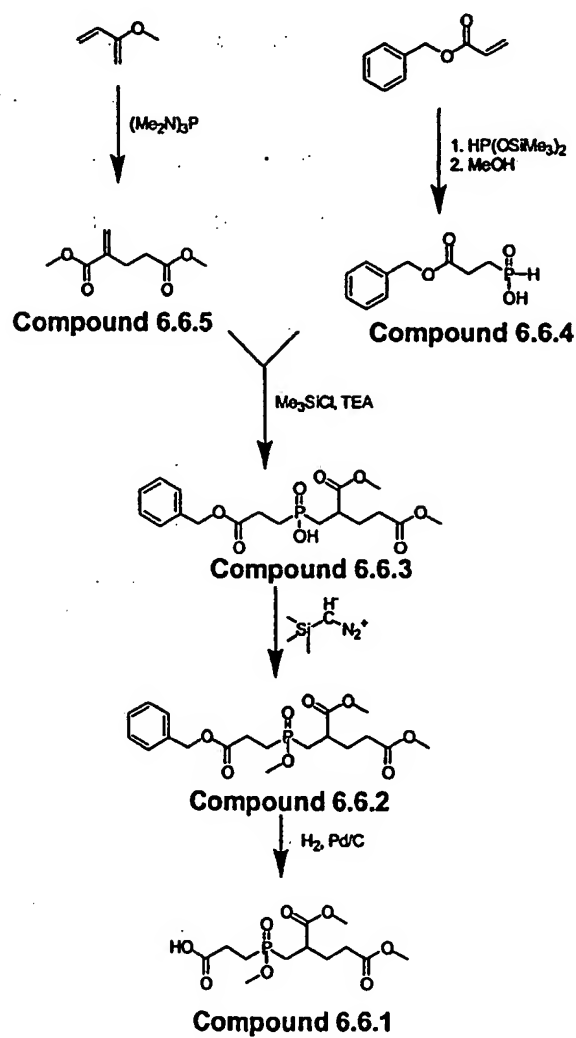
15

Compound 6.2.1b may be prepared by a multistep process. Compound 6.6.1 may be treated with isobutylene and acid (or t-butanol and dicyclohexylcarbodiimide) to give compound 6.2.1b2. The methyl esters may then be hydrolyzed with base. Treatment with (9H-Fluoren-9-yl)-methanol and a condensing agent, such as triisopropylbenzenesulfonyl 3-nitro-1,2,4 triazole and base in an inert solvent will give compound 6.2.1b3. Treatment with acid will cleave the t-butyl ester and give compound 6.2.1b.

20

**Compound 6.6.1****Compound 6.2.1b2****Compound 6.2.1b3**

Compound 6.6.1 has been prepared by the scheme shown below.



Synthesis of compound 6.6.5:

Methyl acrylate, 100 ml was heated till reflux and hexamethylphosphorous triamide (HMPT), 3 ml was added in such a rate that the reaction mixture refluxed gently without heating. At the end the mixture was heated at 115°C for 5 10 min. Vacuum distillation (0.06 mm Hg) afforded 36.7 g, 38% of compound 6.6.5 as clear liquid, which was characterized by ¹H and ¹³C NMR.

Synthesis of compound 6.6.4: A mixture of ammonium hypophosphite, 8.3 g, 0.100 mol and hexamethyldisilazane, 18.3 g, 23.4 ml, 0.113 mol was heated and 10 stirred under reflux and nitrogen until the evolution of ammonia ceased. The mixture was cooled, diluted with 50 ml dichloromethane and benzyl acrylate 14.6 g; 0.090 mol was added drop wise on cooling and stirring in such a rate, that the temperature remained -10 + 0°C. The reaction mixture was left to reach room temperature, treated with 20 ml methanol, diluted with ethyl acetate, and washed 15 with 1 N HCl. After evaporation of the ethyl acetate, silica gel chromatography (5% acetic acid in dichloromethane) afforded 11.25 g, 55% of compound 6.6.4 as a colorless oil, which was characterized by ¹H and ³¹P NMR.

Synthesis of compound 6.6.3:

20 To a solution of compound 6.6.4, 11.25 g, 0.049 mol in 50 ml dichloromethane were added on cooling and stirring under nitrogen at -15°C triethylamine, 5.9 g, 8.12 ml, 0.059 mol, trimethylchlorosilane, 6.4 g, 7.5 ml, 0.059 mol, and compound 6.6.5, 8.44 g, 0.049 mol. Another portion of triethylamine, 5.9 g, 8.12 ml, 0.059 mol, followed by trimethylchlorosilane, 6.4 g, 7.5 ml, 0.059 mol were 25 added in such a rate, that the temperature remained below -10°C. After that the reaction mixture was left overnight at room temperature under nitrogen, diluted

with ethyl acetate, washed with 1 N HCl, brine, and extracted with 5% sodium bicarbonate solution, the sodium bicarbonate extract was acidified to ~pH1 with HCl and extracted with ethyl acetate. Ethyl acetate extract was washed with brine, dried under anhydrous sodium sulfate and evaporated to give 16.7g, 85%
5 of compound 6.6.3 as light yellow oil, which was characterized by ^1H and ^{31}P NMR.

Synthesis of compound 6.6.2:

A solution of compound 6.6.3, 8.0 g, 0.020 mol in methanol, 100 ml was treated
10 on stirring drop wise with a 2 M solution of (trimethylsilyl)diazomethane in hexanes till a stable yellow color (ca. 45 ml). The reaction mixture was diluted with chloroform, 100 ml and washed with 5% sodium bicarbonate and water. Silica gel chromatography with eluant ethyl acetate afforded 5.3 g of compound 6.6.2 as a clear oil, which was characterized by ^1H and ^{31}P NMR.

15

Synthesis of compound 6.6.1:

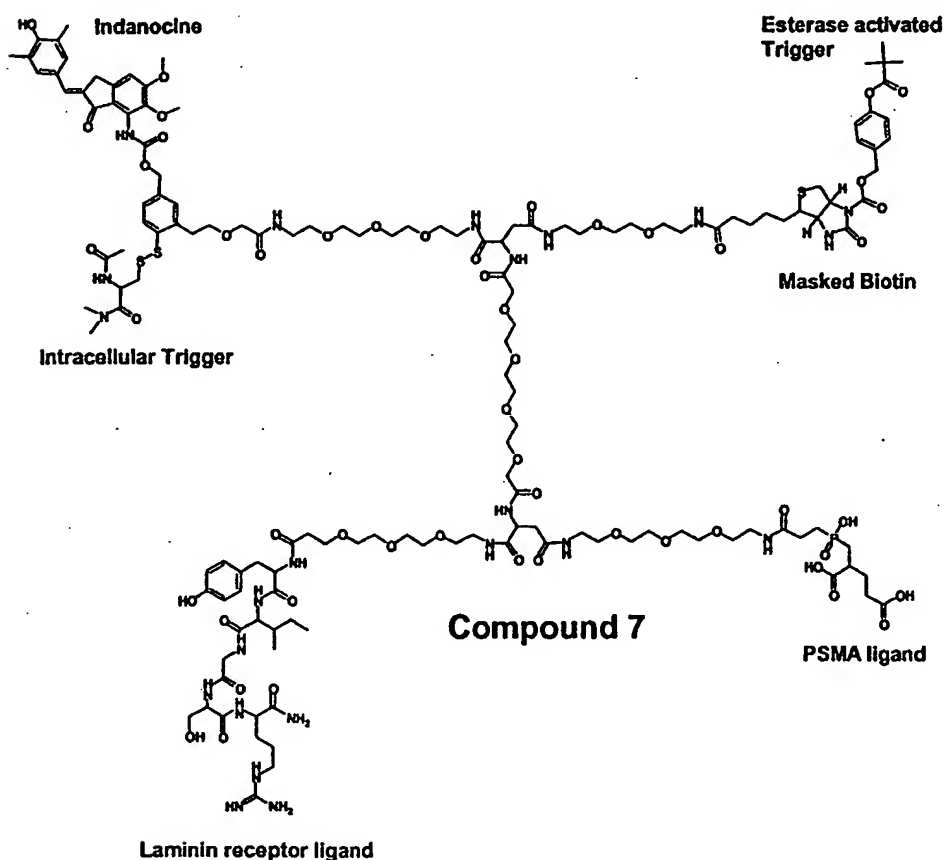
Compound 6.6.2, 6.0 g, 0.014 mol was dissolved in 45 ml methanol and 1 ml acetic acid, and hydrogenated under 600 psi for 72 h in presence of 2.0 g 5% Pd/C in a Parr apparatus. The catalyst was removed by filtration, and the
20 solvent evaporated to give a quantitative yield of compound 6.6.1. The structure and purity of compound 6.6.1 were confirmed by ^1H and ^{31}P NMR.

Compound 6.2.1c is based on a known oligopeptide that is readily synthesized by routine techniques of peptide synthesis. The configuration of the amino acids
25 that comprise compound 6.2.1c are L.

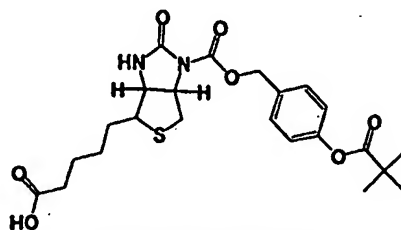
Example 7

Example 7 is a multifunctional drug delivery vehicle that will be selective for prostatic cancer cells that bear both the laminin receptor and PSMA. The drug has a masked biotin moiety as an intracellular transport ligand with a trigger that will be activated by esterase. The toxin indanocine will be liberated following activation of the intracellular trigger by intracellular glutathione or by thioreductases. A wide variety of avidin–intracellular transport ligands may be administered, which will bind to the biotin and transport the drug into the prostate cancer cells by receptor mediated endocytosis.

10

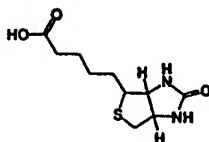


Compound 7 may be synthesized by the methods described for compound 6 by replacing compound 6.2.0b with compound 7.1.

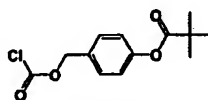


Compound 7.1

- 5 Compound 7.1 may be prepared by treating biotin with a strong base, such as sodium hydride in an inert solvent, such as tetrahydrofuran at low temperature and then reacting with compound 7.1.1 and isolating the product by chromatography. Alternatively, the tetrahydropyranyl ester of biotin may be reacted as described above for biotin and then cleaved by treatment with dilute
- 10 acid.



Biotin

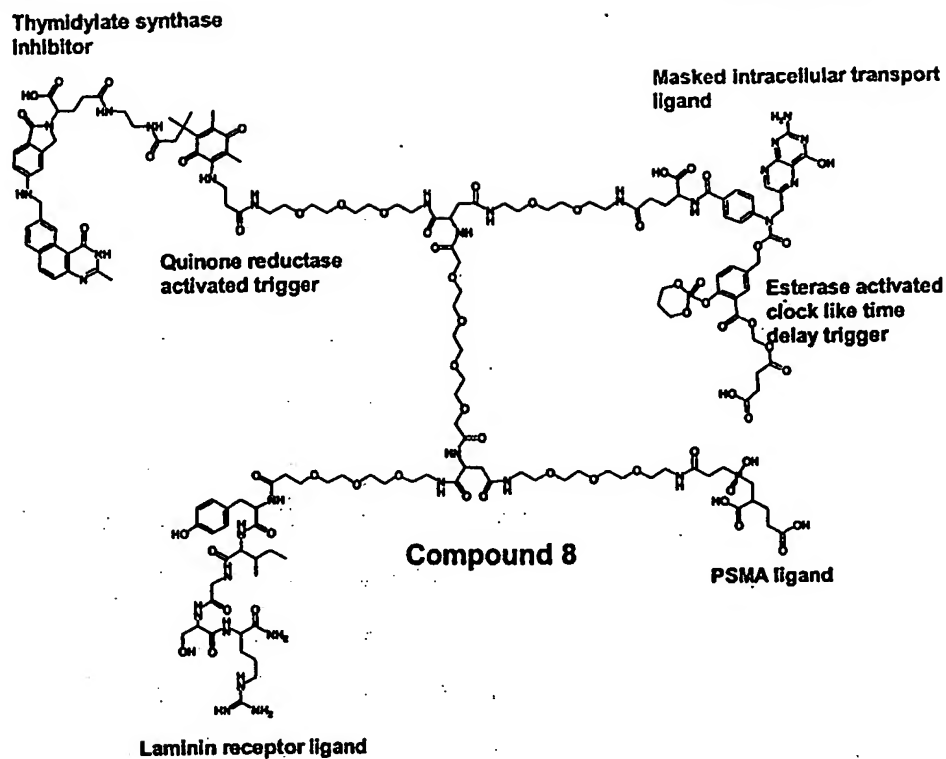


Compound 7.1.1

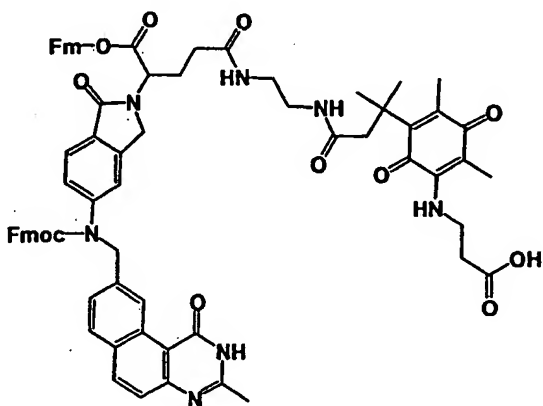
- Compound 7.1.1 is readily prepared by the reaction of 2,2-dimethyl-propionic acid 4-hydroxymethyl-phenyl ester with phosgene in toluene. (Treatment of p-
- 15 hydroxybenzaldehyde with pivaloyl chloride and triethylamine in an inert solvent such as methylene chloride gives 2,2-dimethyl-propionic acid 4-formyl-phenyl ester. Catalytic hydrogenation with palladium on carbon yields 2,2-dimethyl-propionic acid 4-hydroxymethyl-phenyl ester.)

Example 8

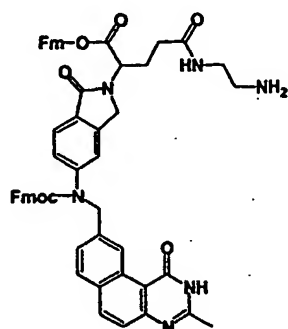
Compound 8 is a multifunctional drug delivery vehicle that will be selective for prostatic cancer cells that bear both the laminin receptor and PSMA. The drug has a masked folic acid moiety as an intracellular transport ligand with a clock
5 like time delay trigger that will be activated by esterase. The N-(2-Amino-ethyl)-amide derivative of the toxin BW1843U89 will be liberated following activation of the intracellular trigger by quinone reductase. BW1843U89 inhibits thymidylate synthase at picomolar concentrations. X-ray crystallography of BW1843U89 bound to *ecoli* thymidylate synthase reveals the carboxylate groups to be free
10 and solvent exposed. Accordingly, the presence of the amino-ethyl group should not impair binding to the thymidylate synthase. The following reference relates to this subject matter: Stout, T.J.; Stroud, R.M., "The Molecular Basis of the Anti-Cancer Therapeutic, BW1843U89, with Thymidylate Synthase at 2.0 Angstroms Resolution," Protein Data Bank (1996) File 1SYN, the contents of which are
15 incorporated herein by reference in their entirety.



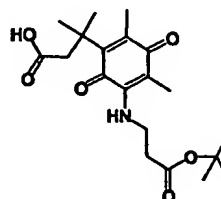
Compound 8 may be synthesized by the methods described for compound 6 by
 5 replacing compound 6.2.0.c with compound 8.1.



Compound 8.1 may be prepared by coupling compound 8.2 and compound 8.3 and then treating with trifluoroacetic acid to cleave the t-butyl ester.

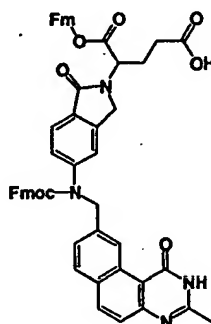


Compound 8.2



Compound 8.3

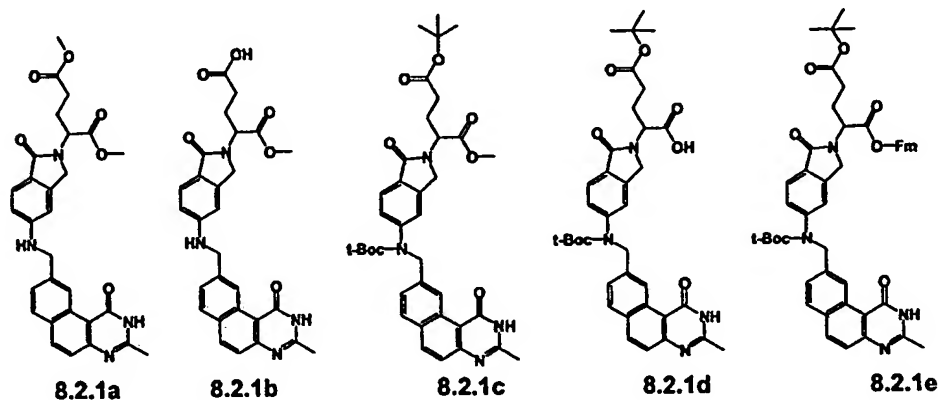
Compound 8.2 as the trifluoroacetate salt, may be prepared by coupling (2-amino-ethyl)-carbamic acid tert-butyl ester with compound 8.2.1 and then removing the t-butyl group with trifluoroacetic acid.



Compound 8.2.1

Compound 8.2.1 may be prepared by a multi-step process. The controlled hydrolysis of compound 8.2.1a with aqueous sodium hydroxide in acetonitrile, followed by acidification and chromatography, gives compound 8.2.1b. Treatment with di-t-butyl pyrocarbonate, t-butanol and dimethylaminopyridine in an inert solvent will give compound 8.2.1c. Treatment with aqueous sodium hydroxide will give compound 8.2.1d. Esterification with 9-H-fluorenyl-9-yl-methanol and a coupling reagent, such as dicyclohexylcarbodiimide, will give

compound 8.2.1e. Treatment with trifluoroacetic acid and then treatment with one equivalent of (9-H-fluorenyl-9-yl)methyloxycarbonyl chloride in presence of base and in inert solvent will give compound 8.2.1.



5

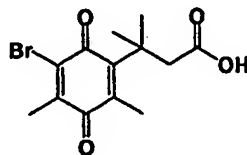
The following references relate to this subject matter: Takeda K., et al.,

"Dicarbonates: Convenient 4-Dimethylaminopyridine Catalyzed Esterification

Reagents," *Synthesis*, 1063-1066 (1994), the contents of which are incorporated

10 herein by reference in their entirety.

Compound 8.3 may be prepared by reacting 3-Amino-propionic acid tert-butyl ester with compound 8.3.1.



Compound 8.3.1

15 The following reference relates to this subject matter: Carpino LA, et al.,

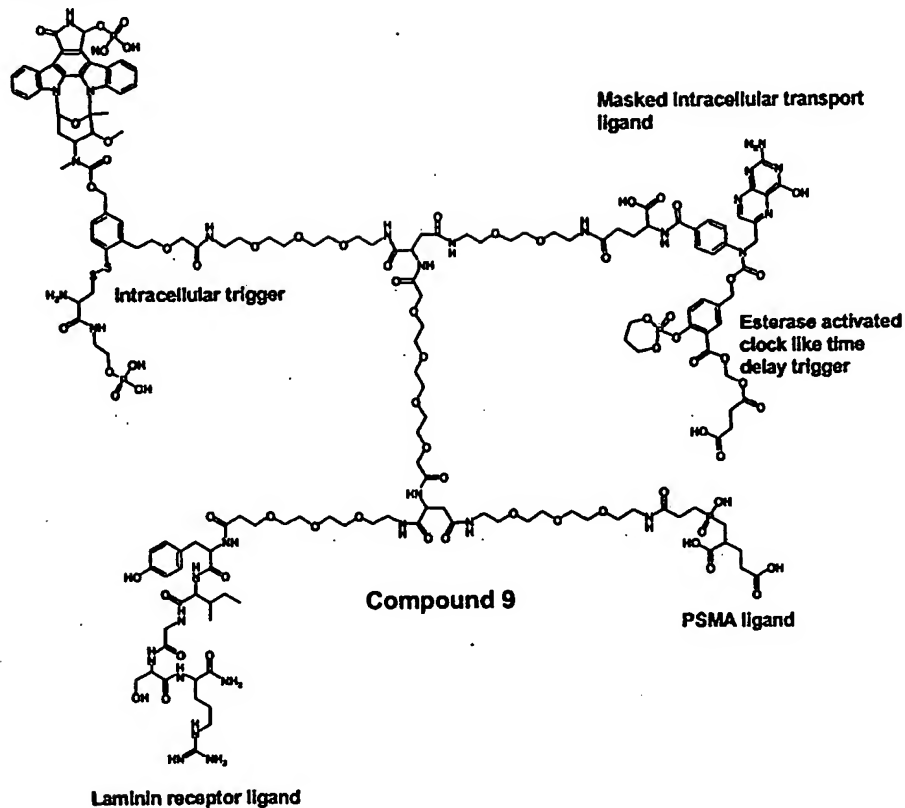
"Reductive Lactonization of Strategically Methylated Quinone Propionic Acid

Esters and Amides," *J Org Chem*, 54:3303-3310 (1989), the contents of which are incorporated herein by reference in their entirety.

5 Example 9

Compound 9 is a multifunctional drug delivery vehicle that will be selective for prostatic cancer cells that bear both the laminin receptor and PSMA. The drug has a masked folic acid moiety, as an intracellular transport ligand with a clock like time delay trigger that will be activated by esterase. Hydroxystaurosporine or

- 10 UCN-01 will be freed upon activation of an intracellular trigger by thiol reductases and hydrolysis of the phosphate group by phosphatases. Hydroxystaurosporine is a potent inhibitor of protein kinases and exhibits synergistic toxicity with a wide range of antineoplastic compounds.

Hydroxystaurosporine

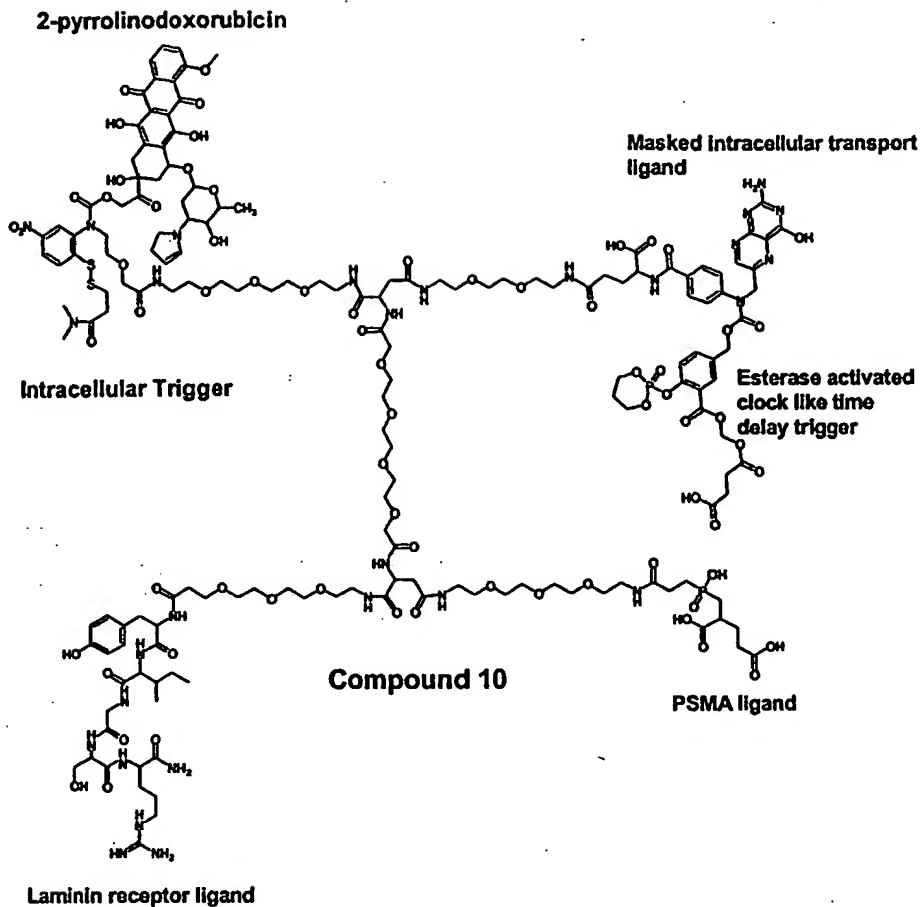
Compound 9 may be prepared by the methods described for compound 6 by replacing compound 6.2.0.c with compound A65.1. (see Example 65)

5

Example 10

Compound 10 a multifunctional drug delivery vehicle with similar targeting specificity to that of compound 9, the highly potent toxin 2-pyrrolinodoxorubicin, will be liberated upon activation of an intracellular disulfide trigger.

10

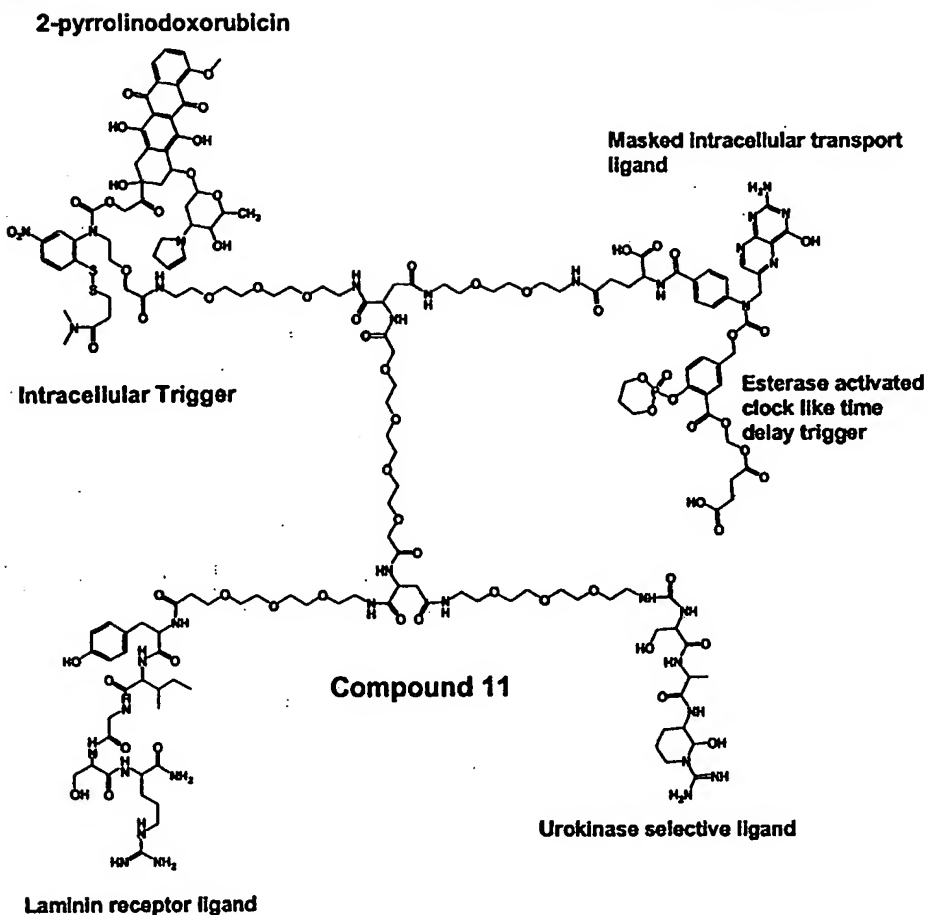


Compound 10 may be prepared by the methods described for compound 6 by replacing compound 6.2.0.c with compound 17.11. (See example 17).

Alternatively, compound 10 may be prepared by a route in which 2-pyrrolinodoxorubicin is coupled in the step just prior to the final deblocking step.

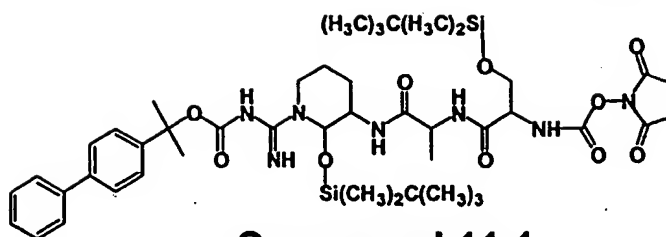
Example 11

Compound 11 is a multifunctional drug delivery vehicle that is similar to compound 10 except it has targeting ligands for urokinase and laminin receptors.



Compound 11 may be prepared by the method described for compound 10 by replacing compound 6.2.1b with compound 11.1 and adding a final deprotection step to remove the silyl protecting groups and treatment with dilute acid to

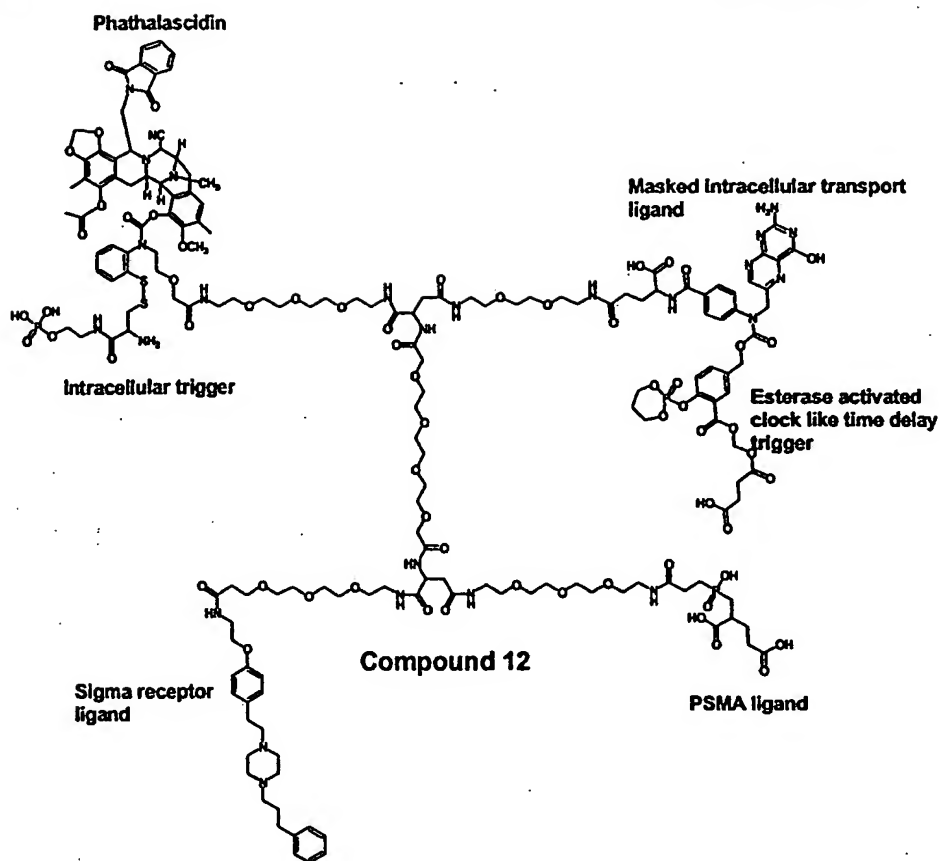
5 remove the 2-Biphenyl-4-yl-propan-2-oxy-carbonyl protecting group. Methods for the cleavage of t-butyl-dimethylsilyl ethers are well known. The following reference relates to this subject matter: Greene, Theodora W.; Wuts, Peter G.M. (1999) "Protective Groups in Organic Synthesis" John Wiley & Sons, Inc. p 133, the contents of which are incorporated herein by reference in their entirety.

**Compound 11.1**

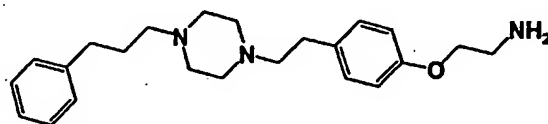
- Compound 11.1 may be prepared by treating compound 14.7.8 with t-butyl-dimethylchlorosilane and base in an inert solvent, followed by treating with base to remove the Fmoc group, followed by treating with N,N'-disuccinimidyl carbonate in an inert solvent in the presence of pyridine.
- 5

Example 12

- Compound 12 is a multifunctional drug delivery vehicle with targeting ligands for PSMA and sigma receptors, both of which are enriched on prostatic cancer cells. The drug will release Phthalascidin a cytotoxin that has an IC_{50} in the 0.1-1 nM range. The phthalascidin is linked to the drug complex by a carbamate group that will undergo cleavage upon reduction of a disulfide bond.
- 10



Compound 12 may be prepared by the methods described for compound 6 by replacing compound 6.2.0.c with compound 21.1.2 and compound 6.2.1c with compound 12.1.



Compound 12.1

Compound 12.1 may be prepared by a multi-step process. Coupling 1-(3-Phenyl-propyl)-piperazine and [4-(2-Azido-ethoxy)-phenyl]-acetic acid (compound 12.1a) will give 2-[4-(2-Azido-ethoxy)-phenyl]-1-[4-(3-phenyl-propyl)-piperazin-1-yl]-ethanone. This may be reduced with a reagent such as aluminum

hydride to give compound 12.1. The following references relate to this subject matter: Zhang Y. et al., "Characterization of Novel N,N'-disubstituted Piperazines as Sigma Receptor Ligands," *J Med Chem*, 41(25):4950-7 (1998), the contents of which are incorporated herein by reference in their entirety.

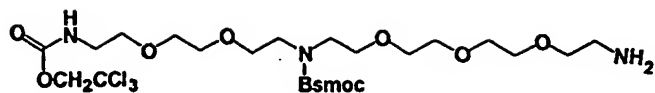
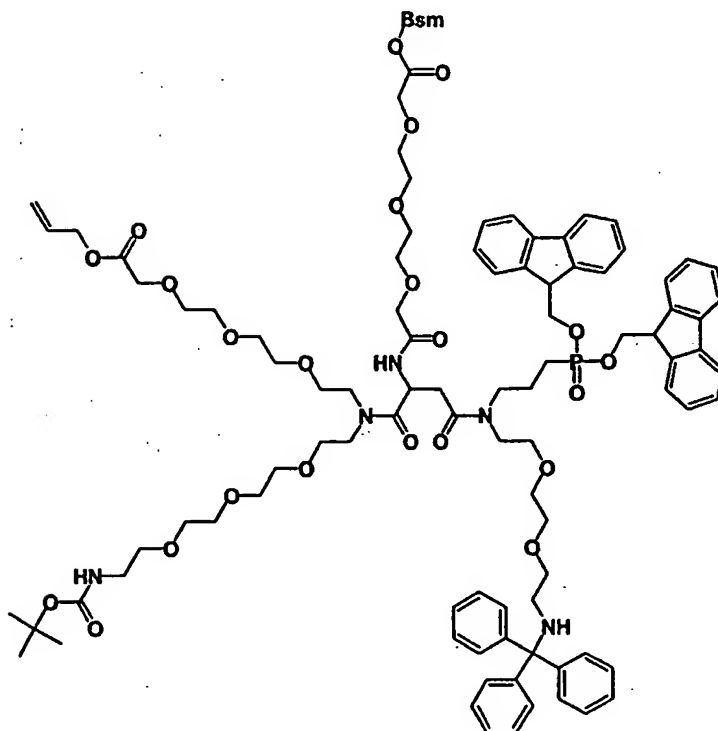
5

Compound 12.1a may be prepared by a multi-step process. Treating (4-Hydroxy-phenyl)-acetic acid methyl ester with one equivalent of strong base and 1 equivalent of ethylene oxide in an inert solvent will give [4-(2-Hydroxy-ethoxy)-phenyl]-acetic acid methyl ester. Treating with tosyl chloride and base in an inert solvent will give {4-[2-(Toluene-4-sulfonyloxy)-ethoxy]-phenyl}-acetic acid methyl ester. Treating with lithium azide in an inert solvent will give [4-(2-Azido-ethoxy)-phenyl]-acetic acid methyl ester. Hydrolysis of the methyl ester will give compound 12.1a.

15

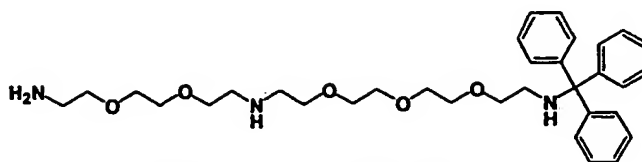
Example 13

Compounds 13a and 13b are an example of a versatile set of linkers that may be employed in the synthesis of a large number of multifunctional drug delivery vehicles. Compound 13a and 13b may be substituted with a large variety of ligands, triggers, and effector groups and then joined together. The linker contains a phosphonate group to increase water solubility of the ultimate multifunctional delivery vehicles.

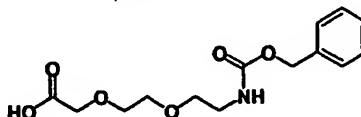
**Compound 13a****Compound 13b**

Compound 13a may be prepared by a multi-step process. Treating {2-[2-(2-Amino-ethoxy)-ethoxy]-ethyl}-[2-(2-[2-(2-(trityl-amino)-ethoxy)-ethoxy]-ethoxy)-ethyl]-amine (Compound 13a.1) with one equivalent of 2,2,2 trichloroethyl N-succinimidyl carbonate in an inert solvent will give [2-(2-[2-(2-(2-[2-(2-(Trityl-amino)-ethoxy)-ethoxy]-ethoxy)-ethylamino]-ethoxy)-ethoxy)-ethyl]-carbamic acid 2,2,2-trichloro-ethyl ester. Treating with (1,1-dioxo-1H-1λ6-benzo[b]thiophen-2-yl)-methyl chloroformate and a base such as pyridine

followed by acid treatment to remove the trityl group will give compound 13a as the salt.



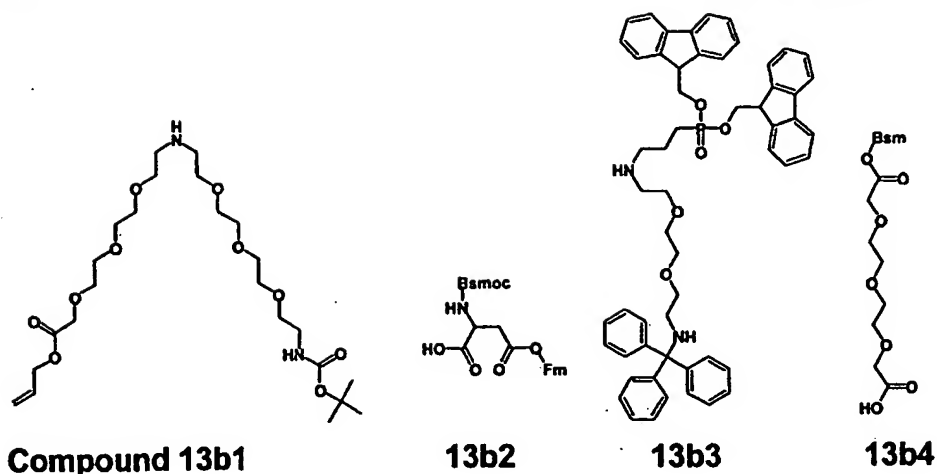
Compound 13a.1



Compound 13a.2

Compound 13a.1 may be prepared by a multi-step process. Treating 2-[2-(2-
 5 Amino-ethoxy)-ethoxy]-ethoxy-ethylamine with one equivalent of trityl chloride
 and base in an inert solvent will give, after purification, 2-[2-(2-[2-(Trityl-amino)-
 ethoxy]-ethoxy)-ethoxy]-ethylamine. This may then be coupled to [2-(2-
 Benzyloxycarbonyl-amino-ethoxy)-ethoxy]-acetic acid (Compound 13.a.2) and
 reduced with an agent such as lithium aluminum hydride in an inert solvent to
 10 give compound 13.a1.

Compound 13a.2 may be prepared by a multi-step process. Oxidation of 2-[2-(2-
 chloro-ethoxy)-ethoxy]-ethanol with Pt on carbon or platinum dioxide in water
 with air will give [2-(2-Chloro-ethoxy)-ethoxy]-acetic acid. Treatment with lithium
 15 azide, followed by catalytic hydrogenation with Pd on carbon, followed by
 reaction with benzyl chloroformate under Schotten-Bauman conditions, will give
 compound 13a.2.



Compound 13b1 and compound 13b2 may be coupled and the product treated
 5 with a hindered base to selectively cleave the Fm ester. The product may then
 be coupled with compound 13b3 and treated with tris(2-aminoethyl) amine to
 cleave the Bsmoc group under conditions that will leave the Fmoc and Fm esters
 intact. The product may then be coupled to compound 13b4 to give compound
 13b. The following references relate to this subject matter: Carpino L.A., et al.,
 10 "New Family of Base- and Nucleophile-Sensitive Amino-Protecting Groups. A
 Michael-Acceptor-Based Deblocking Process. Practical Utilization of the 1,1-
 Dioxobenzo[b]thiophene-2-ylmethyloxycarbonyl (Bsmoc) Group," *J Am Chem*
Soc, 119:9915-9916 (1997); Carpino L.A., et al., "The 1,1-
 Dioxobenzo[b]thiophene-2-ylmethyloxycarbonyl (Bsmoc) Amino-Protecting
 15 Group," *J Org Chem*, 64:4324-4338 (1999), the contents of which are
 incorporated herein by reference in their entirety.

Compound 13b1 may be prepared by a multi-step process. Reacting {2-[2-(2-
 chloro-ethoxy)-ethoxy]-ethoxy}-acetic acid and (2-[2-[2-(2-Amino-ethoxy)-

ethoxy]-ethoxy)-ethyl)-trityl-amine with a base in an inert solvent will give, after purification, [2-(2-[2-(2-[2-(2-[2-(Trityl-amino)-ethoxy]-ethoxy)-ethoxy)-ethylamino]-ethoxy)-ethoxy)-ethoxy]-acetic acid. Treatment with (9H-Fluoren-9-yl)-methyl chloroformate and base in an inert solvent, followed by treatment with dicyclohexylcarbodiimide and allyl alcohol will give {2-[2-(2-((9H-Fluoren-9-yl)methoxycarbonyl)-[2-(2-[2-(2-(trityl-amino)-ethoxy]-ethoxy)-ethoxy)-ethyl]-amino)-ethoxy)-ethoxy]-ethoxy]-acetic acid allyl ester. Treatment with acid followed by treatment with di-t-butyl pyrocarbonate and in an inert solvent will give [2-(2-[2-((2-[2-(2-(2-tert-Butoxycarbonylamino-ethoxy)-ethoxy)-ethoxy)-ethyl)-(9H-fluoren-9-yl)methoxy-carbonyl)-amino]-ethoxy)-ethoxy)-ethoxy]-acetic acid allyl ester. Treatment with base to remove the Fmoc group will give compound 13b1.

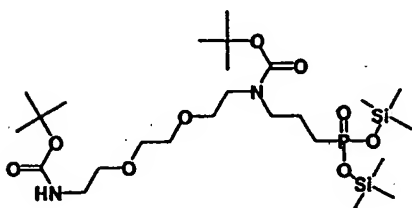
Compound 13b2 may be prepared by treating L-aspartic acid α -t-butyl ester with (1,1-Dioxo-1H-1 λ 6-benzo[b]thiophen-2-yl)-methyl chloroformate and base in an inert solvent or under Schotten-Bauman conditions, and then treating the product with dicyclohexylcarbodiimide and (9H-Fluoren-9-yl)-methanol, and then treating with acid to cleave the t-butyl ester.

Compound 13b3 may be prepared by a multi-step process. Treating [2-(2-Chloro-ethoxy)-ethoxy]-acetic acid with lithium azide in an inert solvent will give [2-(2-Azido-ethoxy)-ethoxy]-acetic acid. Coupling with 3-amino-propan-1-ol will give 2-[2-(2-Azido-ethoxy)-ethoxy]-N-(3-hydroxy-propyl)-acetamide. Reducing with a reagent, such as lithium aluminum hydride in an inert solvent will give 3-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethylamino}-propan-1-ol. Treating with di-t-butyl pyrocarbonate and in an inert solvent will give {2-[2-(2-tert-Butoxycarbonylamino-

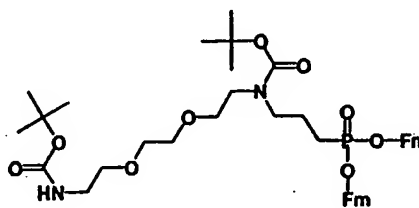
ethoxy)-ethoxy]-ethyl)-(3-hydroxy-propyl)-carbamic acid tert-butyl ester

Treatment with triphenylphosphine and carbon tetrachloride will give {2-[2-(2-tert-Butoxycarbonylamino-ethoxy)-ethoxy]-ethyl)-(3-chloro-propyl)-carbamic acid tert-butyl ester. An Arbuzov reaction with tris (trimethylsilyl) phosphite will give

5 compound 13.b3.1.



Compound 13b3.1



Compound 13b3.2

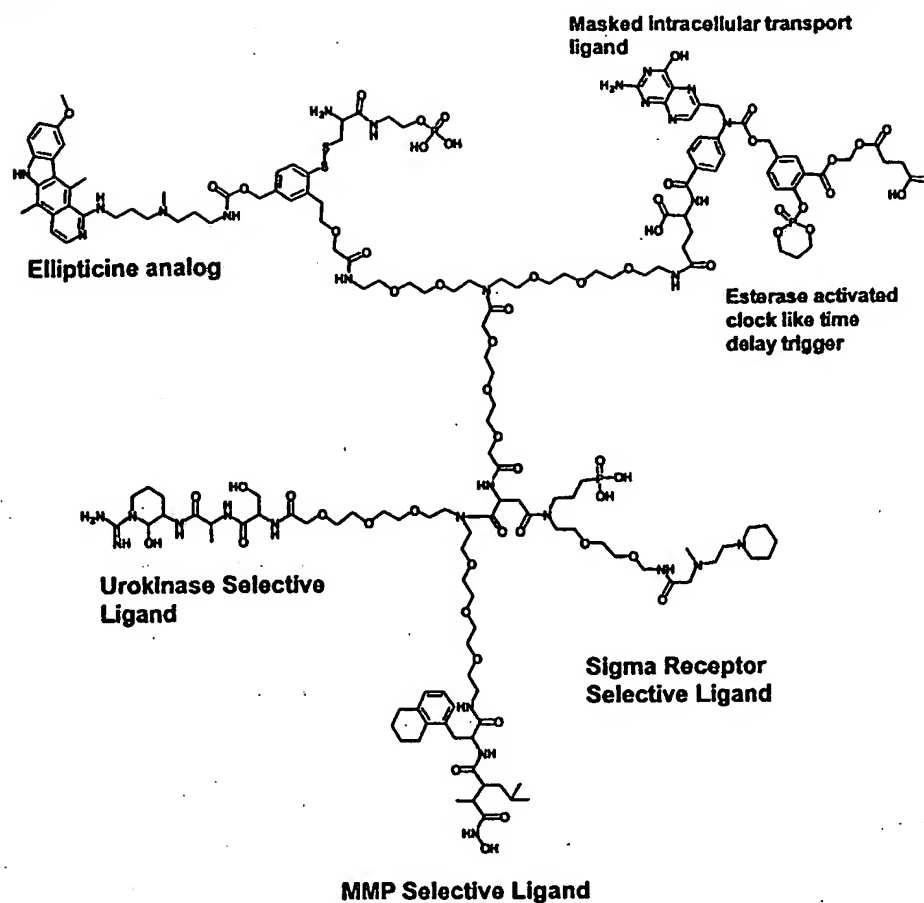
Treating compound 13.b3.1 with oxalyl chloride and a catalytic amount of
 10 dimethylformamide in an inert solvent and removing the chlorotrimethylsilane
 exvacuo will yield the phosphonic dichloride. Reacting with (9H-Fluoren-9-yl)-
 methanol in the presence of a base such as triethylamine will give compound
 13b3.2. Alternatively, the silyl esters may be hydrolyzed and the resulting
 phosphonate may be esterified with (9H-Fluoren-9-yl)-methanol using an agent,
 15 such as triisopropylbenzenesulfonyl 3-nitro-1,2,4 triazole and base in an inert
 solvent to give compound 13b3.2. Treatment with acid will remove the t-Boc
 groups. Treatment with one equivalent of trityl chloride and base in an inert
 solvent will give compound 13b3.

20 Compound 13b4 may be prepared by treating [2-(2-carboxymethoxy-ethoxy)-
 ethoxy]-acetic acid with one equivalent of (9H-Fluoren-9-yl)-methanol and a

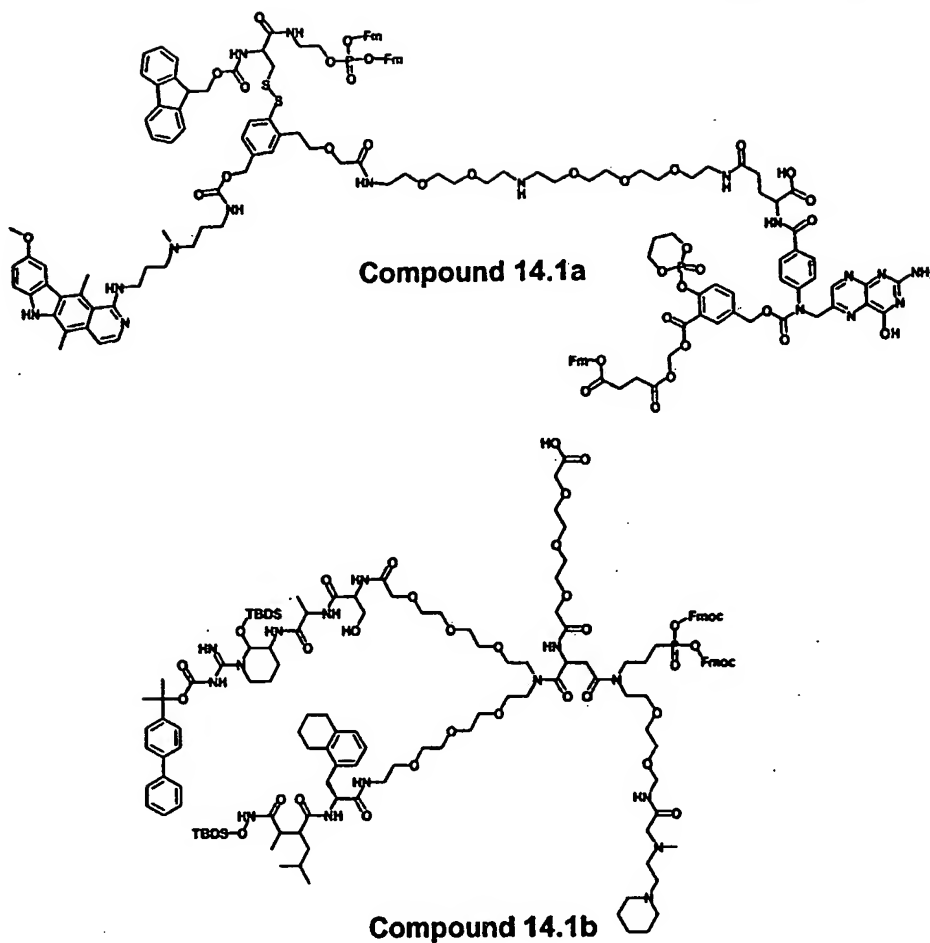
reagent such as dicyclohexylcarbodiimide in an inert solvent, followed by chromatographic separation.

5 Example 14

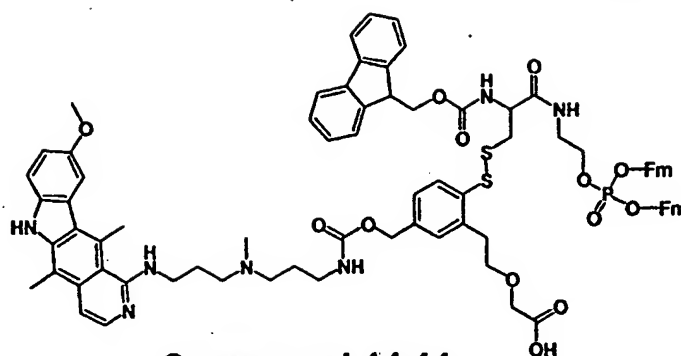
Example 14 is a multifunctional drug delivery vehicle with targeting ligands selective for urokinase, sigma receptors, and matrix metalloproteinases (1,2,3,9, and MT-MMP-1). The drug has a masked folic acid group as intracellular transport ligand with a clock like time delay trigger, which is unmasked by nonspecific esterase. A highly cytotoxic ellipticine analog will be released after activation of an intracellular trigger by thioreductase. The following references relate to this subject matter: Bisagni E., et al., "Synthesis of 1-Substituted Ellipticines by a New Route to Pyrido[4,3-*b*]-carbazoles," *JCS Perkin I*, 1706-1711 (1978); Czerwinski G., et al., "Cytotoxic Agents Directed to Peptide Hormone Receptors: Defining the Requirements for a Successful Drug," *Proc Natl Acad Sci USA*, 95:11520-11525 (1998), the contents of which are incorporated herein by reference in their entirety.

**Compound 14****Synthesis of Compound 14**

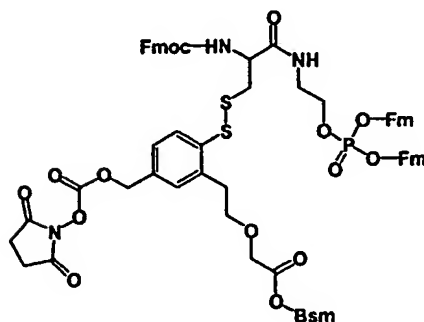
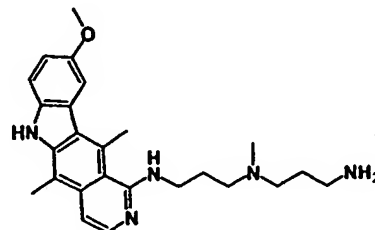
- Compound 14 may be prepared by coupling compound 14.1a and compound
- 5 14.1b and then treating with base to remove the Fm and Fmoc groups, and then treating with a reagent such as tetrabutyl ammonium fluoride or pyridine -HF to remove the silyl protecting groups. The 2-Biphenyl-4-yl-propan-2-oxy-carbonyl protecting group may be removed by treatment with dilute acid.



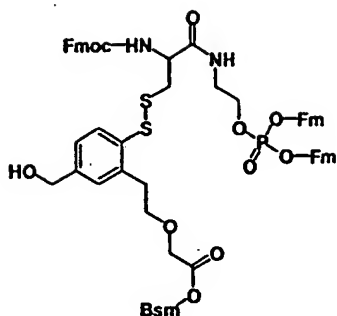
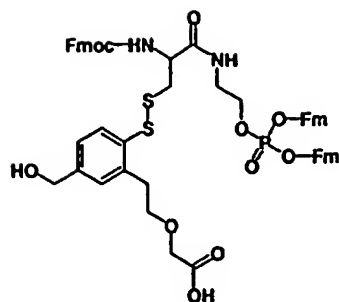
Compound 14.1a may be prepared by a multi-step process. Compound 13a
 5 may be coupled to compound 6.2.0b and then treated with Zn and acid to
 remove the trichloroethoxycarbonyl group. The product may then be coupled to
 compound 14.11. The product may then be treated with tris(2-aminoethyl)amine
 under conditions that will leave the Fmoc and Fm esters intact to give compound
 14.1a.

**Compound 14.11**

Compound 14.11 may be prepared by reacting compound 14.11.1 and
 compound 14.11.2 in an inert solvent and then selectively cleaving the Bsm ester
 5 with tris(2-aminoethyl)amine under conditions that will leave the Fm esters intact.

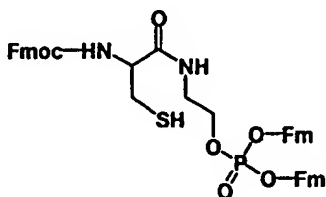
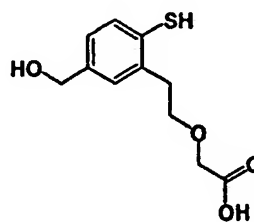
**Compound 14.11.1****Compound 14.11.2**

Compound 14.11.1 may be prepared by reacting the corresponding benzylic
 alcohol (compound 14.11.3) with N,N', disuccinimidyl carbonate in an inert
 10 solvent in the presence of pyridine. The following reference relates to this
 subject matter: Manoharan M., et al., "N-(2
 Cyanoethoxycarbonyloxy)succinimide: A New Reagent for Protection of Amino
 Groups in Oligonucleotides," *J Org Chem*, 63:6468-6472 (1999), the contents of
 which is incorporated herein by reference in its entirety.

**Compound 14.11.3****Compound 14.11.3b**

- Compound 14.11.3 may be prepared by treating compound 14.11.3b with trityl
 5 chloride and a base such as pyridine, and the reacting with
 dicyclohexylcarbodiimide and (1,1-Dioxo-1H-1λ6-benzo[b]thiophen-2-yl)-
 methanol in an inert solvent, and then removing then removing the trityl group
 with acid. .

- 10 Compound 14.11.3b may be prepared by forming the mixed disulfide between
 compound 14.11.4 and compound 6.2.0b2.

**Compound 14.11.4****Compound 6.2.0b2**

- 15 The mixed disulfide may be formed by a variety of methods, such as treatment of
 compound 14.11.4 with one equivalent of sulfonyl chloride and pyridine in an inert

solvent at -78°C to form the the sulfenyl chloride which can then be reacted without isolation at -78°C with compound 6.2.0b2. The following references relate to this subject matter: Derbesy G.; Harpp D.N., "A Simple Method to Prepare Unsymmetrical Di- Tri- and Tetrasulfides," *Tetrahedron Letters*, 5 35(30):5381-5384 (1994), the contents of which are incorporated herein by reference in their entirety.

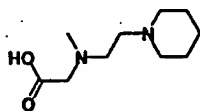
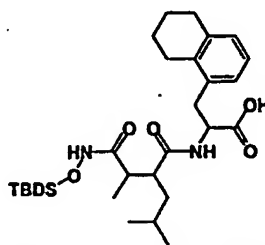
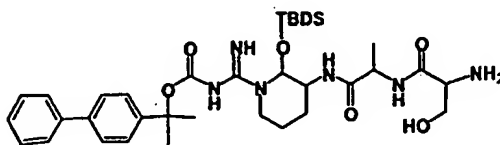
Compound 14.11.4 may be prepared by coupling Fmoc -S- p-methoxytrityl -L- cysteine and 2-amino ethanol, reacting the product with phosphorochloridic acid 10 bis-(9H-fluoren-9-ylmethyl) ester and a base such as triethylamine in an inert solvent, and finally treating with acid to cleave the methoxytrityl protecting group.

Phosphoric acid tris-(9H-fluoren-9-ylmethyl) ester may be prepared by reacting phosphorus oxychloride and (9H-Fluoren-9-yl)-methanol in an inert solvent in the 15 presence of a base such as triethylamine. Treating with one equivalent of a strong base will give phosphoric acid bis-(9H-fluoren-9-ylmethyl) ester.

Treatment with chlorotrimethylsilane and triethylamine in an inert solvent followed by treatment with oxalyl chloride and a catalytic amount of dimethylformamide will give phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) 20 ester.

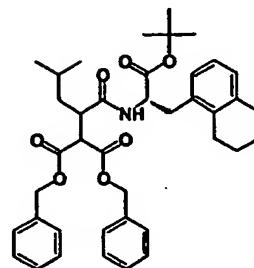
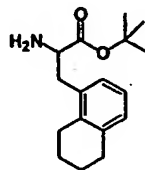
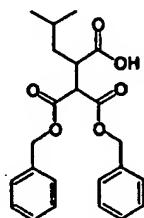
Compound 14.1b may be prepared by a multi-step process. Compound 13b may be treated with acid to selectively remove the trityl group. The product may then be coupled to compound 14.5. The product may then be treated with 25 trifluoroacetic acid to remove the t-Boc group. The product may then be coupled to compound 14.6; the product may then be treated with Pd(0) to cleave the allyl

- ester. The product may then be coupled to compound 14.7. Selectively cleaving the Bsm ester with tris(2-aminoethyl)amine under conditions that will leave the Fm esters intact will give compound 14b. The following references relate to this subject matter: Genêt J.P., et al., "Practical Palladium-Mediated Deprotective
- 5 Method of Allyloxycarbonyl in Aqueous Media," *Tetrahedron*, 50(2):497-503 (1994); Kunz H.; Unverzagt C., "The Allyloxycarbonyl (Aloc) Moiety-Conversion of an Unsuitable into a Valuable Amino Protecting Group for Peptide Synthesis," *Angew Chem Int Ed Engl*, 23 (6):436-437 (1984); Genêt J.P., et al., "A General and Simple Removal of the Allyloxycarbonyl Protecting Group by Palladium-
- 10 Catalyzed Reactions Using Nitrogen and Sulfur Nucleophiles," *Synlett*, 680-682 (1993), the contents of which are incorporated herein by reference in their entirety.

**Compound 14.5****Compound 14.6****Compound 14.7**

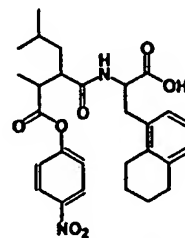
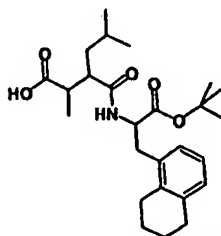
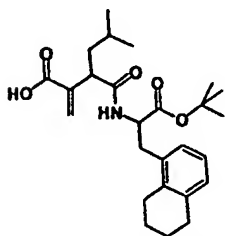
- 15 Compound 14.5 may be prepared by the reaction of ethyl bromoacetate and methyl-(2-piperidin-1-yl-ethyl)-amine followed by hydrolysis of the ethyl ester.

Compound 14.6 may be prepared by a multi-step procedure. Compound 14.6.1 and compound 14.6.2 may be coupled to give 14.6.3.



Compound 14.6.1 Compound 14.6.2 Compound 14.6.3

- Catalytic hydrogenation of compound 14.6.3 followed by treatment with formaldehyde and piperidine will give compound 14.6.4. Catalytic hydrogenation of compound 14.6.4 with Pd will give compound 14.6.5. Esterification with 4-nitrophenol followed by treatment with trifluoroacetic acid to cleave the t-butyl ester will give compound 14.6.6. Treatment with O-tert-butyl(dimethylsilyl)hydroxylamine will give compound 14.6. The following references relate to this subject matter: Yamamoto M., et al., "Inhibition of Membrane-Type 1 Matrix Metalloproteinase by Hydroxamate Inhibitors: An Examination of the Subsite Pocket," *J Med Chem*, 41:1209-1217 (1998), the contents of which are incorporated herein by reference in their entirety.

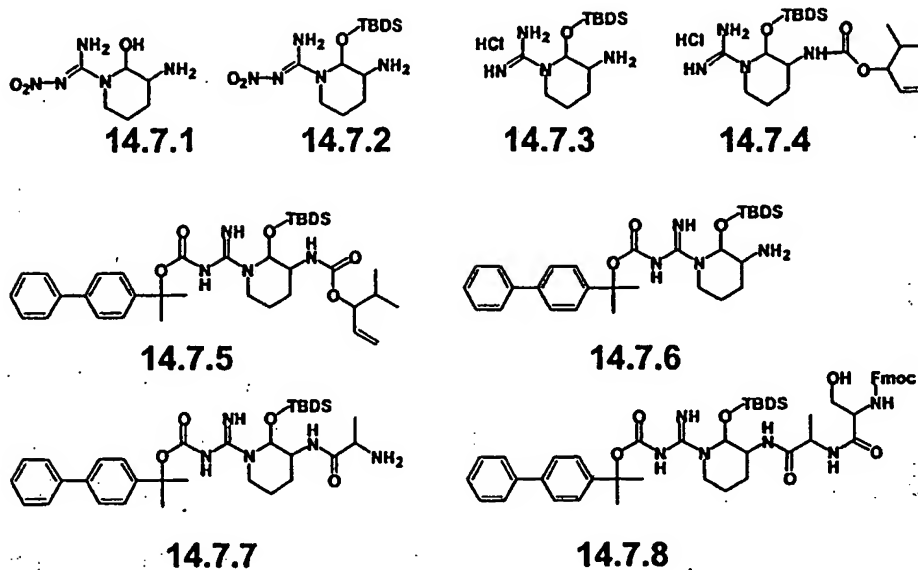


Compound 14.6.4

Compound 14.6.5

Compound 14.6.6

Compound 14.7 may be prepared by a multi-step procedure.



5

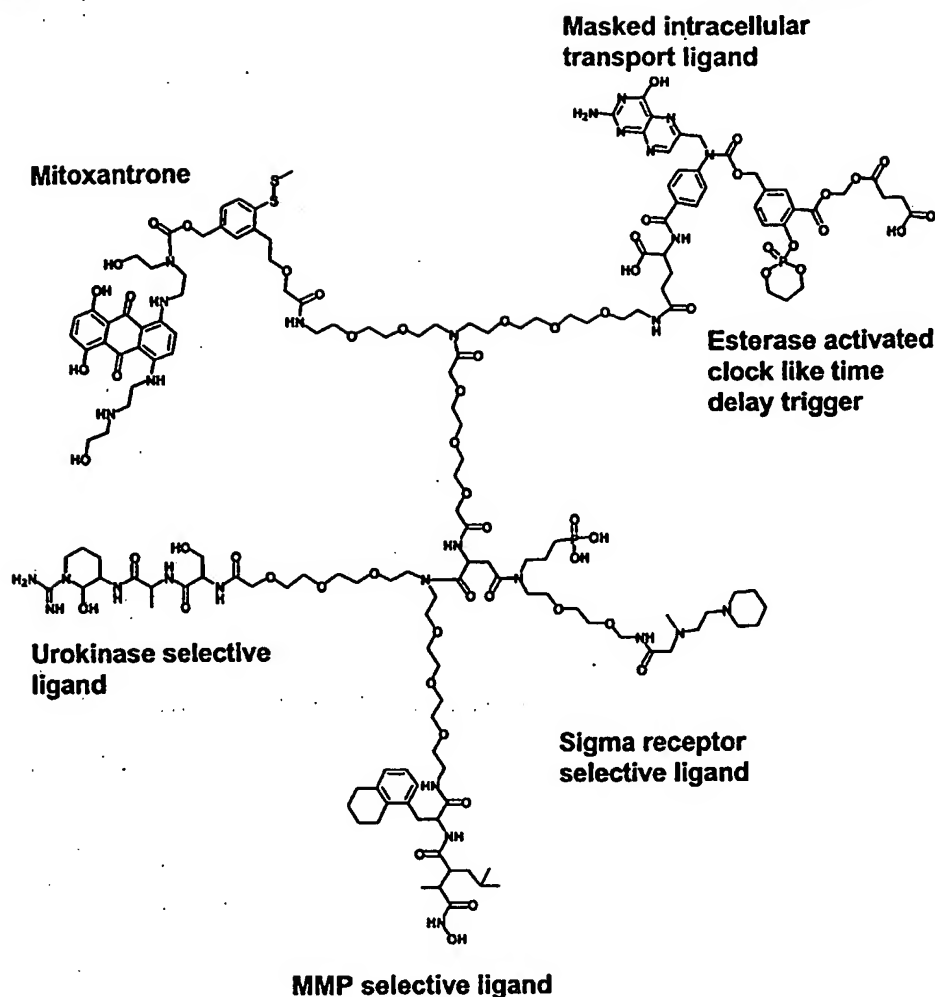
Compound 14.7 may be prepared by a multi-step procedure. Compound 14.7.1 may be treated with t-butyldimethylchlorosilane and base in an inert solvent to give compound 14.7.2. Catalytic hydrogenation with Pd on carbon in the presence of HCl will give compound 14.7.3. Treatment with 4,6-dimethyl-2-(1-
 10 isopropylallyl-oxycarbonylthio)pyrimidine and base in an inert solvent will give compound 14.7.4. Treatment with 1 equivalent of strong base in an inert solvent

and a reagent such as 4-(1-Biphenyl-4-yl-1-methyl-ethoxycarbonyloxy)-benzoic acid methyl ester will give compound 14.7.5. Removal of the isopropylallyloxy-carbonyl protecting group with Pd(0) will give compound 14.7.6. Compound
 15 14.7.6 may then be coupled with Fmoc protected L- alanine and treated with base to remove the Fmoc group and give compound 14.7. Coupling with Fmoc protected D-serine will give compound 14.7.8. Treatment with base to remove

the Fmoc group will give compound 14.7. The following references relate to this subject matter: Tamura S.Y., et al., "Synthesis and Biological Activity of Peptidyl Aldehyde Urokinase Inhibitors," *Bioorg Med Chem Lett*, 10:983-987 (2000); Minami I., et al., "1-Isopropylallyloxycarbonyl (IPAoc) as a Protective Group of Amines and its Deprotection Catalysed by Palladium-Phosphine Complex," *Tetrahedron Let*, 28(24):2737-2740 (1987), the contents of which are incorporated herein by reference in their entirety.

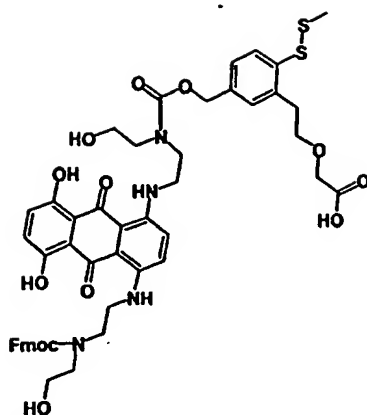
10 Example 15

Compound 15 has targeting specificity similar to compound 14 but releases the highly potent cytotoxin mitoxantrone.

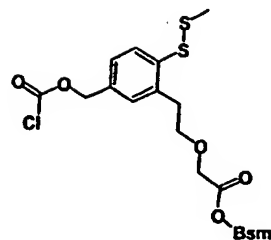
**Compound 15**

Compound 15 may be prepared by the methods described for compound 14 by

5 replacing compound 14.11 with compound 15.1.



Compound 15.1



Compound 15.2

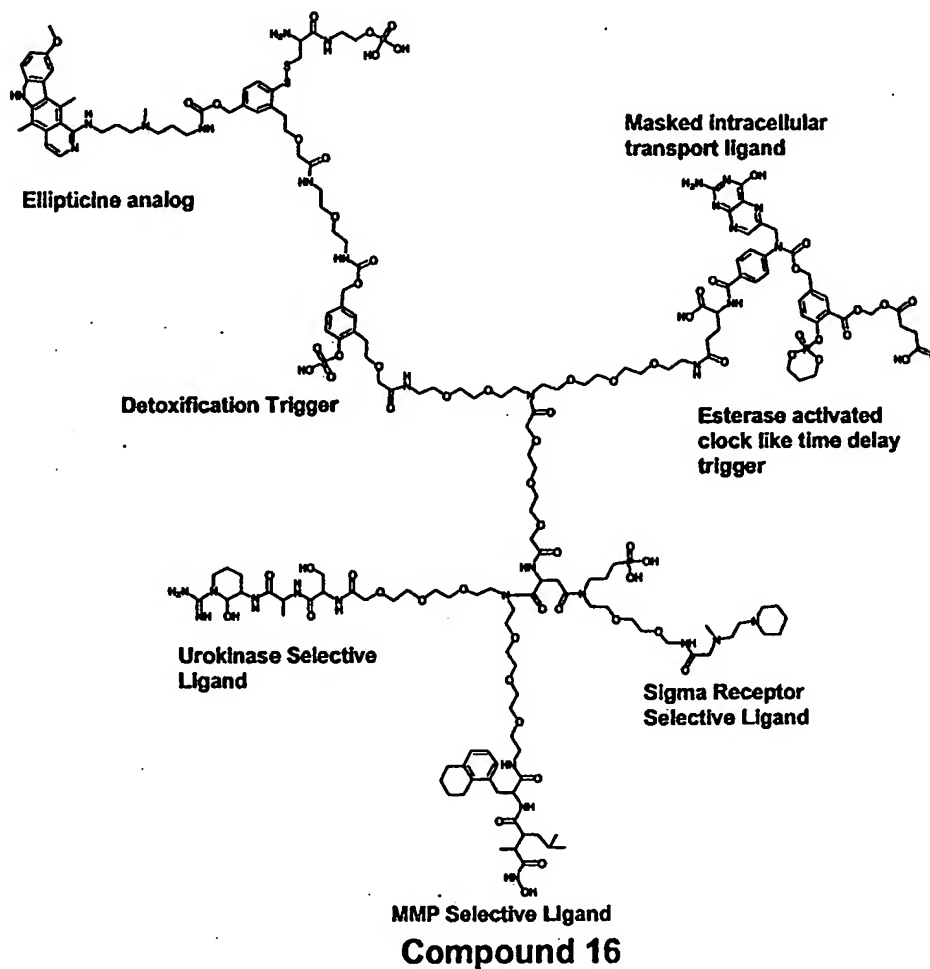
Compound 15.1 may be prepared by reacting mono Fmoc mitoxantrone or ((2-{5,8-dihydroxy-4-[2-(2-hydroxy-ethylamino)-ethylamino]-9,10-dioxo-9,10-dihydro-5-anthracen-1-ylamino}-ethyl)-(2-hydroxy-ethyl)-carbamic acid 9H-fluoren-9-ylmethyl ester) with compound 15.2 in an inert solvent in the presence of a base, such as pyridine, and then treating with tris(2-aminoethyl)amine to cleave the Bsm ester under conditions that will leave the Fmoc group intact.

Compound 15.2 may be prepared by the methods described for the synthesis of compound 6.2.0b1 by replacing N-acetyl -L- cysteine N-N-dimethylamide with methanethiol.

15 Example 16

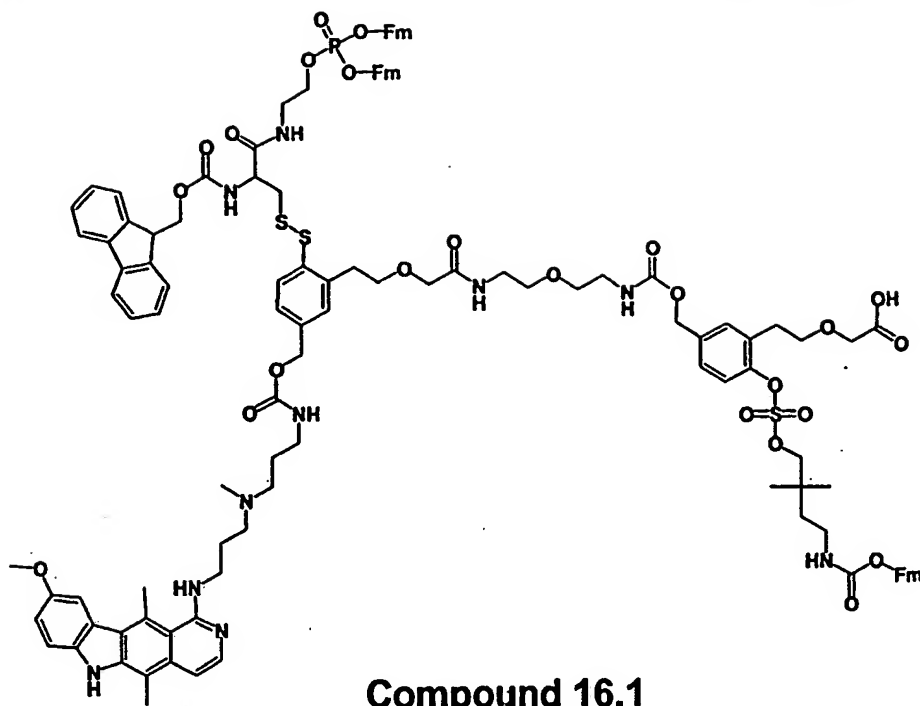
Example 16 is similar to compound 14, but has a detoxification trigger that will be activated by aryl sulfatase. Cleavage of the sulfate ester will trigger the separation of the intracellular trigger - toxin moiety from the intracellular transport group and functionally detoxify the drug. The functional detoxification will result

from impaired cellular penetration of the liberated ionic ellipticine- intracellular trigger complex. This drug may be used with an aryl sulfatase – targeting complex that is specific for vital normal cells.



5

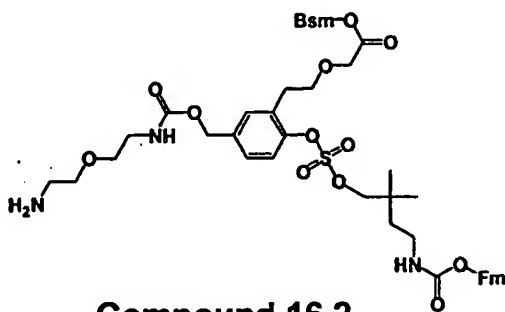
Compound 16 may be prepared by the methods described for compound 14 by replacing compound 14.11 with compound 16.1.



Compound 16.1

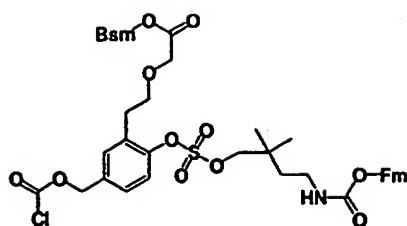
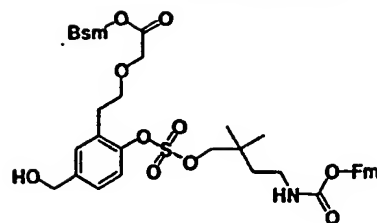
Compound 16.1 may be prepared by coupling compound 16.2 and compound 14.11 and then selectively cleaving the Bsm ester with tris(2-aminoethyl)amine

5 under conditions that will leave the Fm esters intact.



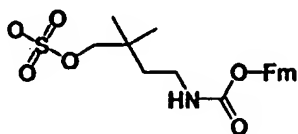
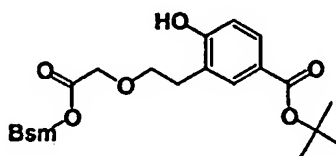
Compound 16.2

Compound 16.2 may be prepared by reacting 2-[2-(Trityl-amino)-ethoxy]-ethylamine and compound 16.3 in an inert solvent in the presence of a base such as pyridine and then treating with acid to remove the trityl protecting group.

**Compound 16.3****Compound 16.4**

Compound 16.3 may be prepared by treating compound 16.4 with phosgene in an inert solvent.

- 5 Compound 16.4 may be prepared by a multi-step process. Compound 16.5 and compound 16.6 may be coupled using a reagent such as dicyclohexylcarbodiimide in an inert solvent. The product may then be treated with trifluoroacetic acid to cleave the t-butyl ester. The product may then be treated with borane in a solvent such as tetrahydrofuran to reduce the carboxylic acid and give compound 16.4.
- 10

**Compound 16.5****Compound 16.6**

- Compound 16.5 may be prepared by reacting 4-Amino-2,2-dimethyl-butan-1-ol with 9-fluorenylmethyl N-succinimidyl carbonate and then treating the product with sulfur trioxide-pyridine in an inert. The following references relate to this subject matter: Roberts J.C., et al., "Neopentyl Ester Protecting Groups for Arylsulfonic Acids," *Tetrahedron Letters*, 38(3):355-358 (1997), the contents of which are incorporated herein by reference in their entirety.
- 15

Compound 16.6 may be prepared by a multi-step process. A Friedel-Crafts reaction between 4-hydroxy-benzoic acid and chlorocarbonylmethoxy acetic acid ethyl ester will give 3-(2-ethoxycarbonylmethoxy acetyl)-4-hydroxy-benzoic acid.

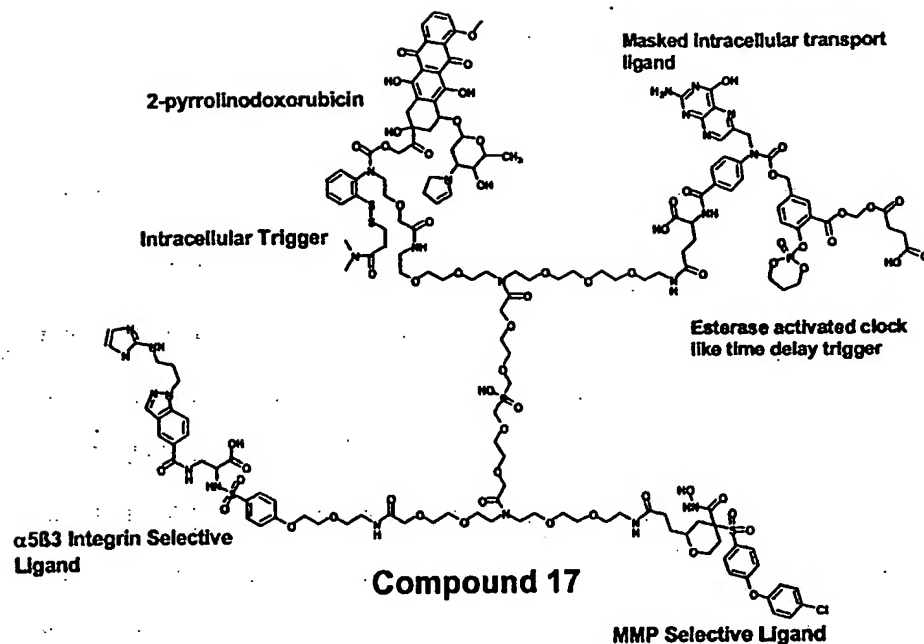
Catalytic reduction with Pd on carbon will give 3-(2-Ethoxycarbonylmethoxy-

- 5 ethyl)-4-hydroxy-benzoic acid. Treatment with acetic anhydride and base will give 4-acetoxy-3-(2-ethoxycarbonylmethoxy-ethyl)-benzoic acid. Treatment with di-t-butyl pyrocarbonate, t-butanol and dimethylaminopyridine in an inert solvent will give 4-acetoxy-3-(2-ethoxycarbonylmethoxy-ethyl)-benzoic acid tert-butyl ester. Treatment with sodium hydroxide, followed by HCl, will give 3-(2-
- 10 Carboxymethoxy-ethyl)-4-hydroxy-benzoic acid tert-butyl ester. Treatment with trifluoroacetic anhydride and base will give 3-(2-Carboxymethoxy-ethyl)-4-(2,2,2-trifluoro-acetoxy)-benzoic acid tert-butyl ester. Coupling to (1,1-Dioxo-1H-1 λ 6-benzo[b]thiophen-2-yl)-methanol using a reagent such as dicyclohexylcarbodiimide will give 3-[2-(1,1-Dioxo-1H-1 λ 6-benzo[b]thiophen-2-
- 15 ylmethoxycarbonylmethoxy)-ethyl]-4-(2,2,2-trifluoro-acetoxy)-benzoic acid tert-butyl ester. Hydrolysis of the trifluoroacetate ester will give compound 16.6.

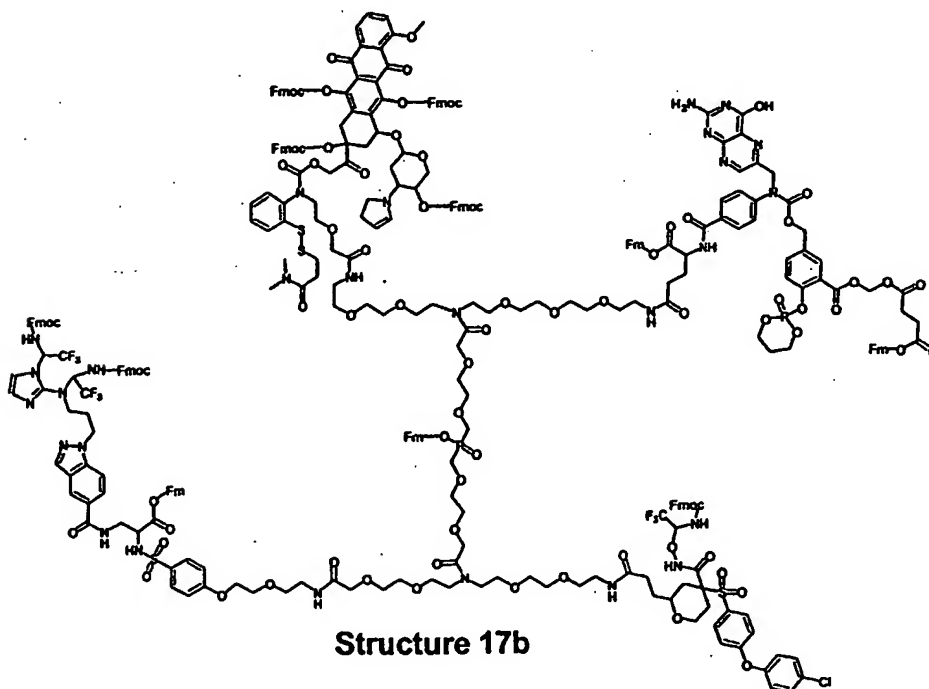
20 Example 17

- Compound 17 is a multifunctional delivery vehicle which will target tumor cells that are positive for both $\alpha 5\beta 3$ integrin, and MMPs 2, 3, 9, 12, and 13. The drug has a masked folic acid moiety as an intracellular transport ligand. The highly
- 25 intracellular disulfide trigger. Cleavage of the disulfide by thiol reductases will unmask a thiol group, which will, via an intramolecular nucleophilic reaction,

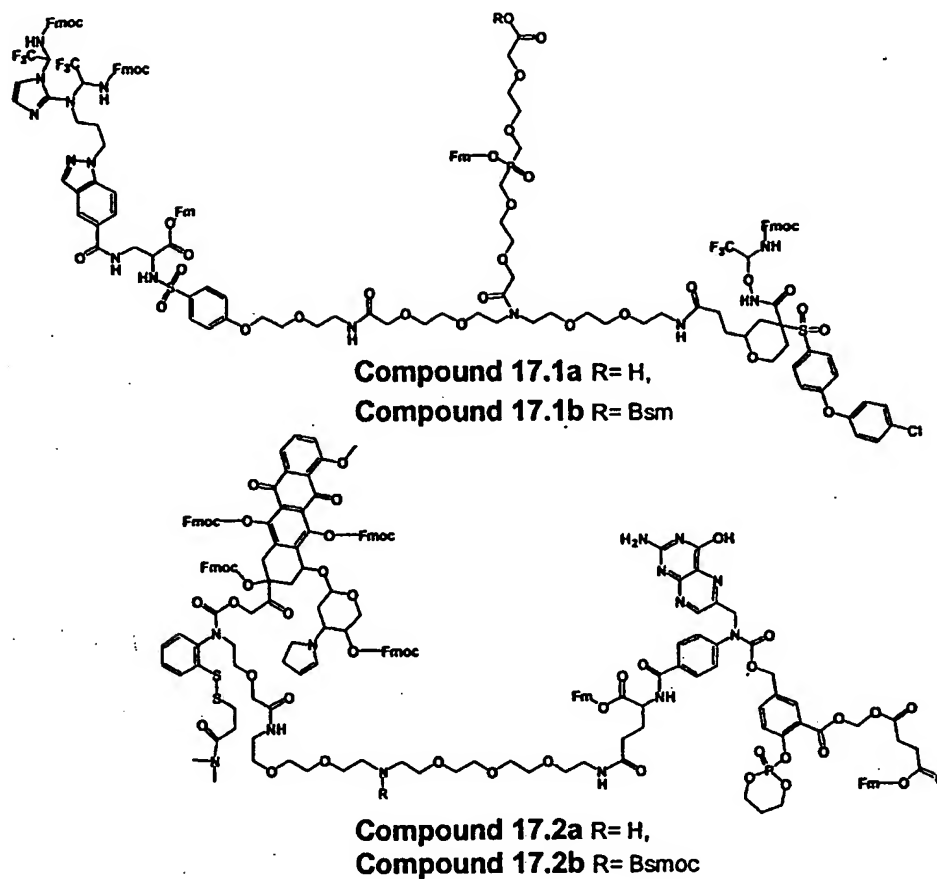
cleave the carbamate group and release the toxin. The following references relate to this subject matter: Batt D.G., et al., "Disubstituted Indazoles as Potent Antagonists of the Integrin $\alpha_v\beta_3$," *J Med chem*, 43:41-58 (2000); Nagy A., et al., "High Yield Conversion of Doxorubicin to 2-pyrrolinodoxorubicin, an Analog 500-
5 1000 Times More Potent: Structure-Activity Relationship of Daunorubicin-Modified Derivatives of Doxorubicin," *Proc Natl Acad Sci USA*, 93:2464-2469 (1996); WO99/25687, 5/27/99, Williams R.A., et al., "Aromatic Sulfone Hydroxamic Acid Metalloprotease Inhibitor"; 5,932,595, 8/03/99, Bender et al., "Matrix Metalloprotease Inhibitors"; Lovejoy B., et al., "Crystal Structures of
10 MMP-1 and -13 Reveal the Structural Basis for Selectivity of Collagenase Inhibitors," *Nat Struct Biol*, 6(3):217-21 (1999); Botos I., et al., "Structure of Recombinant Mouse Collagenase-3 (MMP-13)," *J Mol Biol*, 292:837-844 (1999); Hutchins J.E.C.; Fife T.H., "Fast Intramolecular Nucleophilic Attack by Phenoxide Ion on Carbamate Ester Groups," *J Am Chem Soc*, 95(7):2282-2286 (1973); Fife
15 T.H., et al., "Highly Efficient Intramolecular Nucleophilic Reactions. The Cyclization of *p*-Nitrophenyl *N*-(2-Mercaptophenyl)-*N*-methylcarbamate and Phenyl *N*-(2-Aminophenyl)-*N*-methylcarbamate," *J Am Chem Soc*, 97(20):5878-5882 (1975), the contents of which are incorporated herein by reference in their entirety.



Compound 17 may be prepared by treating structure 17b with base to cleave the Fmoc and related fluorenylmethyl esters (Fm) groups.

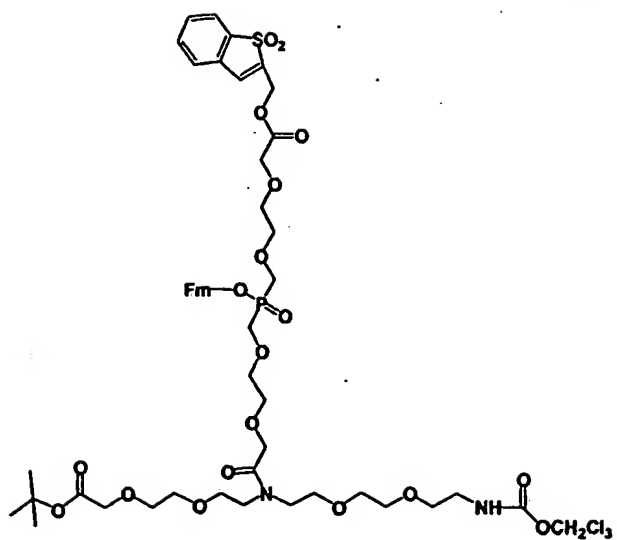
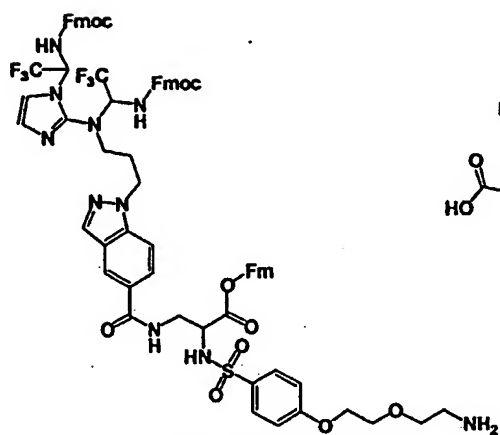
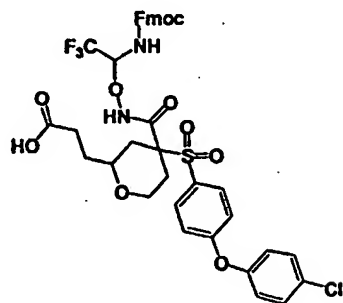


Compound 17b may be prepared by coupling compounds 17.1a and 17.2a.

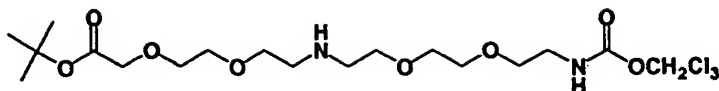


Compound 17.1a and 17.2a may be prepared by treatment of 17.1b and 17.2b
 5 with tris(2-aminoethyl)amine under conditions that will leave the Fmoc and Fm
 esters intact.

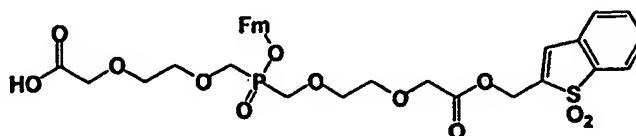
Compound 17.1b may be prepared in a multi-step procedure. Treating
 compound 17.4 with trifluoroacetic acid will selectively deblock the t-butyl ester
 10 group. The product may then be coupled to compound 17.5. Next, the 2,2,2
 trichloroethoxycarbonyl protecting group may be selectively removed with Zn and
 acid. Then the product may be coupled to compound 17.6 to give compound
 17.1b.

**Compound 17.4****Compound 17.5****Compound 17.6**

Compound 17.4 may be prepared by coupling compound 17.7 and 17.8.



Compound 17.7



Compound 17.8

Compound 17.7 may be prepared by treating [2-(2-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethylamino}-ethoxy)-ethoxy]-acetic acid tert-butyl ester (compound 17.7a) with 2,2,2-trichloroethyl N-succinimidyl carbonate in an inert solvent.

5

Compound 17.7a may be prepared by reacting [2-(2-Chloro-ethoxy)-ethoxy]-acetic acid tert-butyl ester with 2-[2-[2-(trityl-amino)-ethoxy]-ethoxy]-ethylamine in the presence of base in an inert solvent, isolating the product and then selectively removing the trityl group with acid.

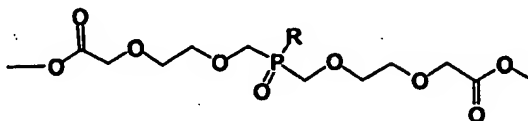
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[2-(2-Chloro-ethoxy)-ethoxy]-acetic acid may be prepared by oxidizing 2-[2-(2-chloro-ethoxy)-ethoxy]-ethanol. This may be carried out by catalytic oxygenation with Pt on carbon or platinum dioxide in water with air. The t-butyl ester may be prepared using routine methods well known to one skilled in the arts. The following references relate to this subject matter: Tsou K.C., et al., "Synthesis of 5-Fluoro-2'-deoxyuridine-5'-carboxylic Acid and Its Derivatives," *J Med Chem*, p.173 (1969), the contents of which are incorporated herein by reference in their entirety.

2-[2-(2-(trityl-amino)-ethoxy)-ethoxy]-ethylamine may be made by treating trityl chloride with amino)-ethoxy]-ethoxy)-ethylamine and isolating the monosubstituted product.

- 5 Compound 17.8 may be prepared in a multistep synthesis. Compound 17.8.1a may be prepared by reacting one equivalent of (2-Chloromethoxy-ethoxy)-acetic acid methyl ester and bis(trimethylsilyl)phosphonite, silylating the product, and without isolation, reacting with an additional equivalent of (2-Chloromethoxy-ethoxy)-acetic acid methyl ester. The following references relate to this subject
- 10 matter: Boyd E.A.; Regan A.C., "Synthesis of Alkyl Phosphinic Acids from Silyl Phosphonites and Alkyl Halides," *Tetrahedron Letters*, 35(24):4223-4226 (1994), the contents of which are incorporated herein by reference in their entirety.

- (2-Chloromethoxy-ethoxy)-acetic acid methyl ester may be prepared by
- 15 chloromethylation of 2-Hydroxy-ethoxy)-acetic acid methyl ester with HCL and paraformaldehyde.



Compound 17.8.1a R = trimethylsilyloxy

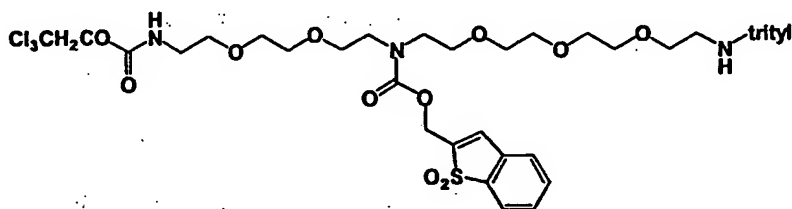
Compound 17.8.1b R = Cl

Compound 17.8.1c R = (9H-Fluoren-9-yl)-methoxy

- 20 Compound 17.8.1a may be treated with thionyl chloride to give compound 17.8.1b. Reaction with 9-H- fluorenyl-9-yl-methanol and a base, such as triethylamine, will give compound 17.8.1c. Hydrolysis of the methyl esters by

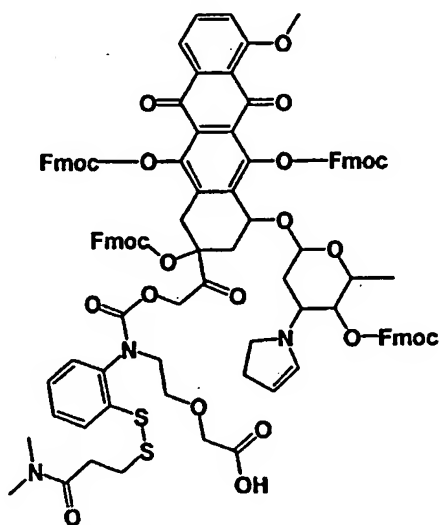
esterase or with a catalyst such as distannoxane, followed by coupling of 1 equivalent of 1,1-Dioxobenzo[*b*]thiophene-2-yl-methanol, with dicyclohexylcarbodiimide will give compound 17.8 after purification.

- 5 Compound 17.2b may be prepared in a multi-step procedure.



Compound 17.9

- Treating compound 17.9 with acid will remove the trityl group. The product may then be coupled with compound 6.2.0b. The trichloroethoxycarbonyl group may then be removed with Zn and acid. The product may then be coupled to compound 17.11 to give compound 17.2b.
- 10



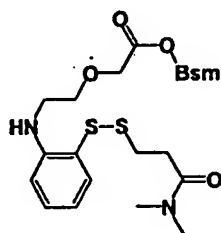
Compound 17.11

Compound 17.11 may be prepared by reacting compound 17.11.1 and compound 17.11.2 in an inert solvent in the presence of a base, such as pyridine, and then cleaving the Bsm ester with tris(2-aminoethyl)amine under conditions that will leave the Fmoc groups intact.

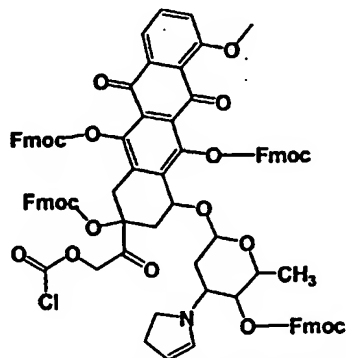
5

In an alternate method, compound 17.11.1 may be treated with phosgene in a solvent, such as toluene at low temperature to generate the carbamoyl chloride derivative, which may then be reacted with 2-pyrrolinodoxirubicin in the presence of a base such as pyridine. In this case, the Fmoc protection of the 2-

10 pyrrolinodoxirubicin need not be employed.



Compound 17.11.1



Compound 17.11.2

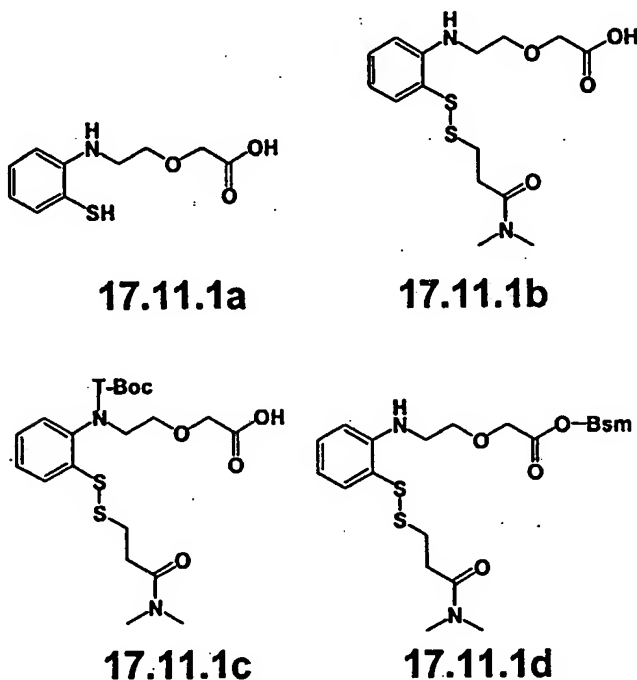
Compound 17.11.1 may be prepared by a multi-step process. Reacting diethyl azidocarboxylate with and 3-mercapto-N,N-dimethyl-propionamide and then reacting the product with compound 17.11.1a will form the mixed disulfide compound 17.11.1b. The following references relate to this subject matter:

15 Mukaiyama T.; Takahashi K., "A Convenient Method for the Preparation of Unsymmetrical Disulfides by the use of Diethyl Azodicarboxylate," *Tetrahedron Letters*, 56:5907-5908 (1968), the contents of which are incorporated herein by

20 reference in their entirety.

Treating compound 17.11.1b with di-t-butyl pyrocarbonate and in an inert solvent will give compound 17.11.1c. Treating with (1,1-Dioxo-1H-1l6-benzo[b]thiophen-2-yl)-methanol and a reagent such as dicyclohexylcarbodiimide in an inert solvent, followed by acid treatment to cleave the t-Boc group, will give compound

5 17.11.1d.



Compound 17.11.1a may be prepared by a multi-step procedure. 2-

Aminophenyl-disulfide may be reacted with (2-Oxo-ethoxy)-acetic acid methyl

10 ester in the presence of a dehydrating agent to form the Schiff base. The imine may then be reduced with a reagent such as sodium borohydride to give compound 17.11.1a.

The compound (2-Oxo-ethoxy)-acetic acid methyl ester may be prepared in a

15 multi-step procedure. Treating [1,4]Dioxane-2,6-dione with methanol and

dimethylaminopyridine will give methoxycarbonylmethoxy-acetic acid. This may then be converted into chlorocarbonylmethoxy-acetic acid methyl ester by treatment with thionyl chloride. The acid chloride may then be reduced to the desired aldehyde with lithium tri-tert-butoxyaluminum hydride at low temperature

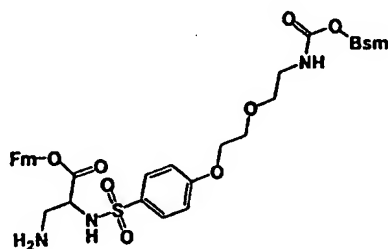
5 in an inert solvent.

Compound 17.11.2 may be prepared by a multi-step process. Treating 2-pyrrolinodoxorubicin in an inert solvent with 1 equivalent of 1,1-dioxobenzo[b]thiophene-2-yl-methoxycarbonyl chloride and a base such as

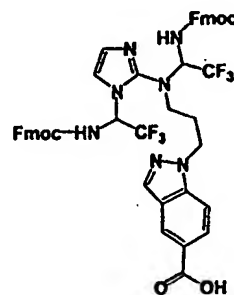
10 pyridine will protect the primary hydroxy group on C14. The product may then be treated with 4 equivalents of 9-H- fluorenyl-9-yl-methoxycarbonyl chloride and a base such as pyridine. The product may then be treated with tris(2-aminoethyl)amine to selectively remove the 1,1-dioxobenzo[b]thiophene-2-yl-methoxycarbonyl protecting group. The product may then be treated with

15 phosgene to give the chloroformate (compound 17.11.2).

Compound 17.5 may be prepared by coupling compound 17.5.1 and compound 17.5.2 and then removing the 1,1-dioxobenzo[b]thiophene-2-yl-methoxycarbonyl protecting group with tris(2-aminoethyl)amine.

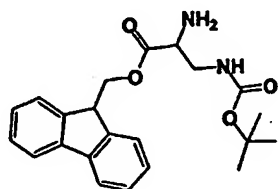


Compound 17.5.1

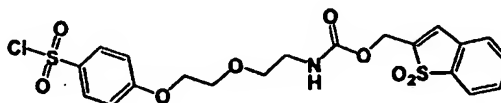


Compound 17.5.2

Compound 17.5.1 may be made by reacting compound 17.5.1a and 17.5.1b, in an inert solvent, in the presence of a base such as pyridine and then removing the t-Boc group with trifluoroacetic acid.

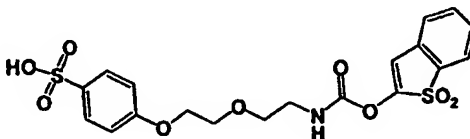


Compound 17.5.1a



Compound 17.5.1b

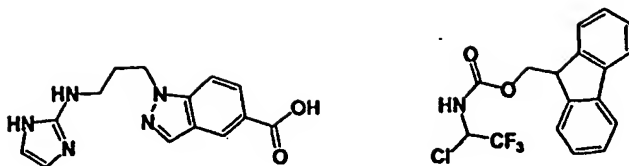
- 5 Compound 17.5.1a may be prepared from (S) 3-Amino-2-benzyloxycarbonylamino-propionic acid. Treatment with di-t-butyl dicarbonate will give 2-benzyloxycarbonylamino-3-tert-butoxycarbonylamino-propionic acid. Catalytic hydrogenation, followed by treatment with 2,2,2 trichloroethyl chloroformate and base, will give 3-tert-Butoxycarbonylamino-2-(2,2,2-trichloroethoxycarbonylamino)-propionic acid. Coupling with (9H-Fluoren-9-yl)-methanol will give 3-tert-Butoxycarbonylamino-2-(2,2,2-trichloro-ethoxycarbonylamino)-propionic acid 9H-fluoren-9-yl methyl ester. Treatment with Zn and acid will remove the trichloroethylcarbonyl protecting group and give compound 17.5.1a.
- 15 Compound 17.5.1b may be prepared by treating compound 17.5.1c with a reagent such as thionyl chloride.



Compound 17.5.1c

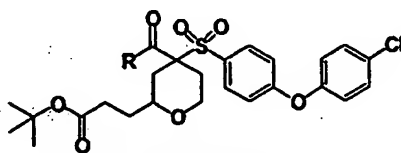
Compound 17.5.1c may be prepared by a multi-step procedure. Reacting 4-hydroxy-benzenesulfonic acid and 1-(2-Azido-ethoxy)-2-chloro-ethane in the presence of base will give 4-[2-(2-azido-ethoxy)-ethoxy]-benzenesulfonic acid. Reduction of the azido group by catalytic hydrogenation will give 4-[2-(2-amino-ethoxy)-ethoxy]-benzenesulfonic acid. Treatment with 1,1-dioxobenzo[b]thiophene-2-yl-methoxycarbonyl chloride and a base such as pyridine will give compound 17.5.1c.

- Compound 17.5.2 may be prepared by treating 1-[3-(1H-Imidazol-2-ylamino)-propyl]-1H-indazole-5-carboxylic acid (compound 17.5.2a) with 2 equivalents of (1-Chloro-2,2,2-trifluoro-ethyl)-carbamic acid 9H-fluoren-9-ylmethyl ester (compound 17.5.2b) and base in an inert solvent. Compound 17.5.2b may be prepared by reacting carbamic acid 9H-fluoren-9-ylmethyl ester with trifluoroacetaldehyde and then treating with phosphorous trichloride in an inert solvent.
- The following references relate to this subject matter: Batt D.G., et al., "Disubstituted Indazoles as Potent Antagonists of the Integrin $\alpha_v\beta_3$," *J Med Chem*, 43:41-58 (2000); Weygand F., et al., "2,2,2-Trifluoro-1-acylaminoethyl Groups as Protective Groups for Imino Groups of Histidine in Peptide Synthesis," *Chem Ber*, 100(12):3841-9 (1967); Weygand, Friedrich; Steglich, Wolfgang; Pietta, Pier G., *Chem Ber*, 99: p.1944 (1966), the contents of which are incorporated herein by reference in their entirety.



Compound 17.5.2a Compound 17.5.2b

Compound 17.6 may be prepared by treating compound 17.6.1a with acid to remove the tert-butoxy group. Alternatively, esterase may be employed.



Compound 17.6.1a R = -OCH(CF₃)NH-Fmoc

Compound 17.6.1b R = Cl

Compound 17.6.1c R = OH

Compound 17.6.1d R = methoxy

5

Compound 17.6.1a may be prepared by treating compound 17.6.1b with O-trimethylsilyl protected hydroxylamine and base in an inert solvent, followed by hydrolysis of the silyl protecting group, followed by treatment with (1-Chloro-2,2,2-trifluoro-ethyl)-carbamic acid 9H-fluoren-9-ylmethyl ester and base.

10

Alternate synthetic approaches would be to react the hydroxamate with 4,4'-dimethoxytrityl chloride or 4-methoxytritylchloride, or pixyl chloride instead of (1-Chloro-2,2,2-trifluoro-ethyl)-carbamic acid 9H-fluoren-9-ylmethyl ester. These protecting groups may be removed at the end of the synthesis with dilute acid under conditions that do not cleave the acetal of the doxorubicin group.

15

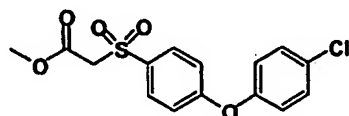
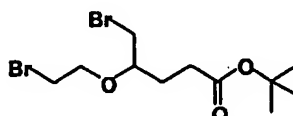
Compound 17.6.1.b may be prepared by the treatment of the carboxylic acid derivative 17.6.1c with well known agents for the synthesis of acid chlorides such as triphenylphosphine/carbon tetrachloride, or thionyl chloride, or oxalyl chloride and dimethylformamide in inert solvents.

5

Compound 17.6.1c may be prepared by the selective hydrolysis of the methyl ester in compound 17.6.1d with aqueous sodium hydroxide.

Compound 17.6.1d may be prepared by the alkylation of compound 17.6.2 with compound 17.6.3 using a base such as sodium hydride in an inert solvent. The following reference relates to this subject matter: WO99/25687, 5/27/99, Williams R.A., et al., "Aromatic Sulfone Hydroxamic Acid Metalloprotease Inhibitor", the contents of which is incorporated herein by reference in its entirety.

15

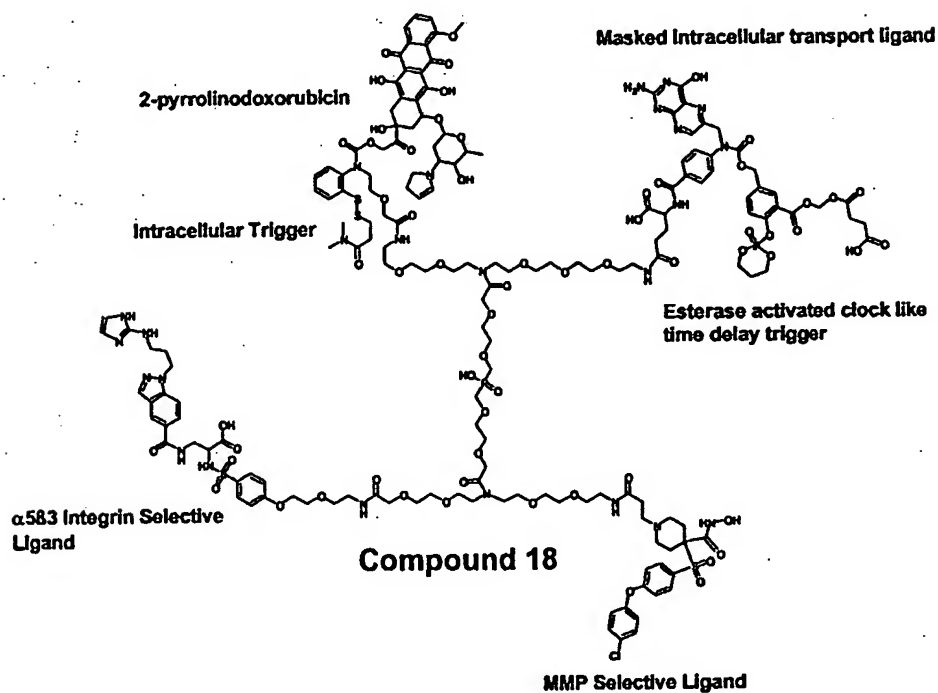
**Compound 17.6.2****Compound 17.6.3**

Compound 17.6.3 may be prepared by a multi-step procedure. Treating 5-hydroxy-tetrahydro-pyran-2-one with one equivalent of ethylene oxide in the presence of a strong base such as potassium tert-butoxide in an inert solvent will give, after purification by chromatography, 5-(2-Hydroxy-ethoxy)-tetrahydro-pyran-2-one. Treatment with HBr, followed by trimethylbromosilane in an inert solvent, will give 5-bromo-4-(2-bromo-ethoxy)-pentanoic acid after hydrolysis of the silyl ester. The tert-butyl ester (compound 17.6.3) may then be prepared by

treatment with an excess of iso-butylene, catalyzed with strong acids, such as para-toluenesulfonic acid.

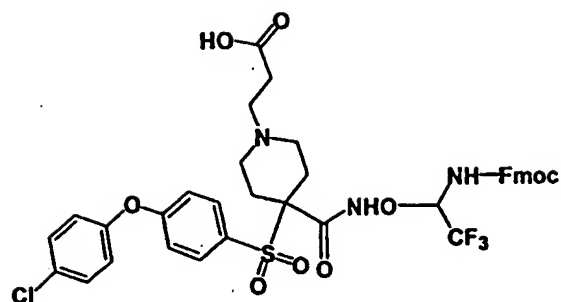
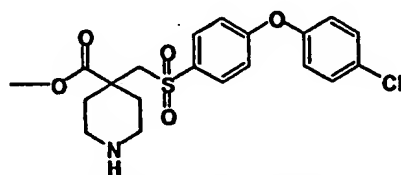
5 Example 18

Compound 18 is similar to compound 17 in its targeting specificity. The difference is in the MMP selective ligand.



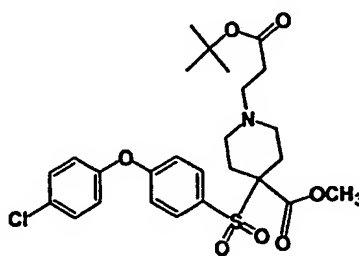
10

Compound 18 may be prepared using the procedures as described for compound 17 by replacing compound 17.6 with compound 18.1.

**Compound 18.1****Compound 18.2**

Compound 18.1 may be prepared by a multi-step procedure. Alkylating compound 18.2 with t-butyl 3-bromopropanoate in the presence of base, in an inert solvent, will give compound 18.3. The following references relate to this

5 subject matter: EP0 780 386 A1 6/25/97 Bender S.L., "Matrix Metalloprotease Inhibitors", the contents of which are incorporated herein by reference in their entirety.

**Compound 18.3**

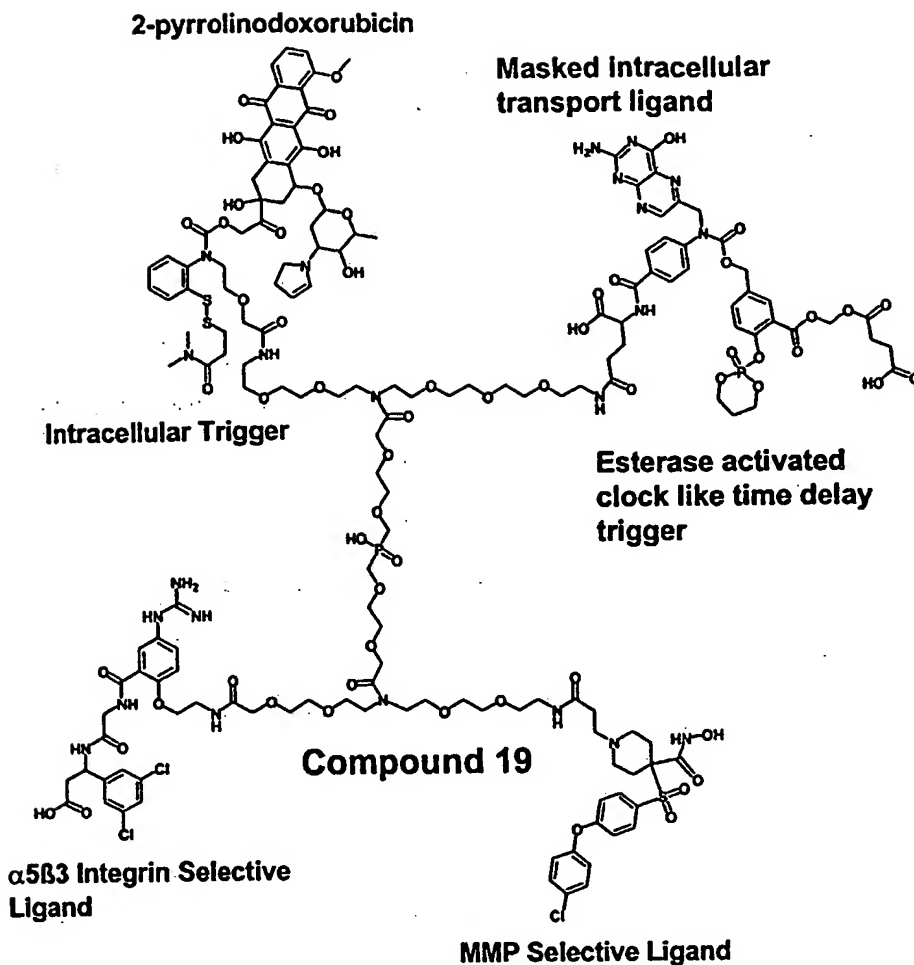
Compound 18.3 may be transformed into compound 18.1 using the same reaction procedures described to transform compound 17.6.1d into compound 17.6.

5

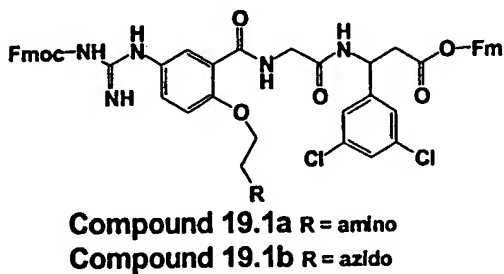
Example 19

Compound 19 is similar to compound 18, however a different $\alpha 5 \beta 3$ integrin selective ligand is employed. The following references relate to this subject matter: WO 96-US13500 1997 Ruminski P.G., et al., "Preparation of Meta-
10 Guanidine, Urea, Thiourea or Azacyclic Amino Benzoic Acid Derivatives as Integrin Antagonists"; Carron C.P., et al., "A Peptidomimetic Antagonist of the Integrin $\alpha v \beta 3$ Inhibits Leydig Cell Tumor Growth and the Development of Hypercalcemia of Malignancy," *Cancer Res*, 58(9):1930-1935 (1998), the contents of which are incorporated herein by reference in their entirety.

15



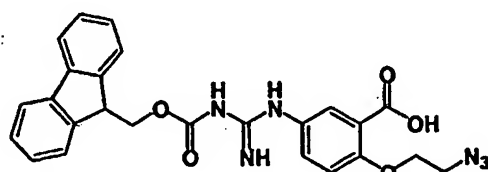
Compound 19 may be prepared using the procedures described for compounds 17 and compounds 18 by substituting compound 19.1a for compound 17.5.



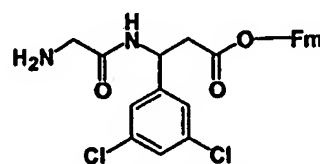
- 5 Compound 19.1a may be prepared by the reduction of the azido compound 19.1b with triphenylphosphine and water in an inert solvent. The following references relate to this subject matter: Pak J. K.; Hesse M., "Synthesis of 671

Penta-*N*-Protected Homocaldopentamine and Its Selective Acylation," *J Org Chem*, 63:8200-8204 (1998), the contents of which are incorporated herein by reference in their entirety.

- 5 Compound 19.1b may be prepared by coupling compound 19.2 and compound 19.3.

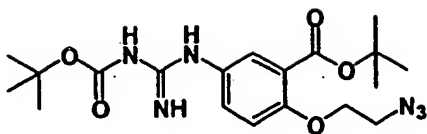
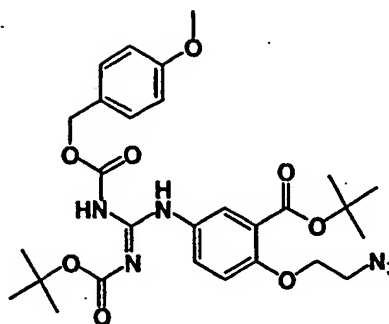


Compound 19.2



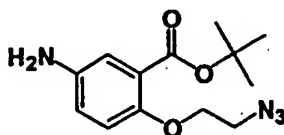
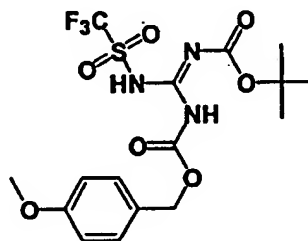
Compound 19.3

- Compound 19.2 may be prepared by treating compound 19.4 with 9H-fluoren-9-ylmethyl chloroformate and a base such as pyridine and catalytic amounts of dimethylaminopyridine, and then treating with acid to remove the t-Boc and t-butyl ester groups. Compound 19.4 may be prepared by the selective removal of the p-methoxybenzyloxycarbonyl protecting group from compound 19.5 with dilute trifluoroacetic acid in an inert solvent. The following references relate to
- 15 this subject matter: Wang S.S., et al., "4-Methoxybenzyloxycarbonyl Amino Acids in Solid Phase Peptide Synthesis," *Int J Peptide Protein Res*, 30:662-667 (1987), the contents of which are incorporated herein by reference in their entirety.

**Compound 19.4****Compound 19.5**

Compound 19.5 may be prepared by reacting compound 19.6 and compound 19.7 in the presence of a base such as triethylamine in an inert solvent.

5

**Compound 19.6****Compound 19.7**

Compound 19.7 may be prepared by a multi-step procedure. Treating guanidine hydrochloride with base and one equivalent of a reagent such as 2-(4-methoxybenzyloxycarbonyloxyimino)-2-phenyl acetonitrile, followed by additional base and 1 equivalent of di-t-butyl dicarbonate, followed by treatment with NaH and triflic anhydride in an inert solvent will give compound 19.7. The following references relate to this subject matter: Feichtinger K., et al., "Diprotected Triflylguanidines: A New Class of Guanidinylation Reagents," *J Org Chem*,

63:3804-3805 (1998), the contents of which are incorporated herein by reference in their entirety.

Compound 19.6 may be prepared by a multi-step procedure. The compound 2-

5 Hydroxy-5-nitro-benzoic acid may be treated with pivaloyl chloride and a base in an inert solvent to give 2-(2,2-Dimethyl-propionyloxy)-5-nitro-benzoic acid.

Treatment with isobutylene and an acid will give 2-(2,2-dimethyl-propionyloxy)-5-nitro-benzoic acid tert-butyl ester. Treatment with aqueous sodium hydroxide will give, after neutralization, 2-hydroxy-5-nitro-benzoic acid tert-butyl ester.

10 Treatment with one equivalent of a strong base and one equivalent of ethylene oxide in an inert solvent will give 2-(2-Hydroxy-ethoxy)-5-nitro-benzoic acid tert-butyl ester. Reduction of the nitro group by catalytic hydrogenation with Pd catalysis will give 5-Amino-2-(2-hydroxy-ethoxy)-benzoic acid tert-butyl ester.

Treatment with 2-(4-methoxybenzyloxycarbonyloxyimino)-2-phenyl acetonitrile
15 and base will give compound 19.6a. Treatment with tosyl chloride in an inert solvent with a base such as pyridine will give Compound 19.6b. Treatment with lithium azide in an inert solvent such as dimethylformamide will give compound 19.6c. The selective removal of the p-methoxycarbonyl protecting group with 10% trifluoroacetic acid in methylene chloride will give compound 19.6.

20

Compound 19.3 may be prepared by a multi-step procedure. Treating 3-amino-3-(3,5-dichloro-phenyl)-propionic acid with di-t-butyl dicarbonate and then coupling with (9H-Fluoren-9-yl)-methanol and dicyclohexylcarbodiimide, followed by deprotection of the amino group with trifluoroacetic acid will give 3-Amino-3-

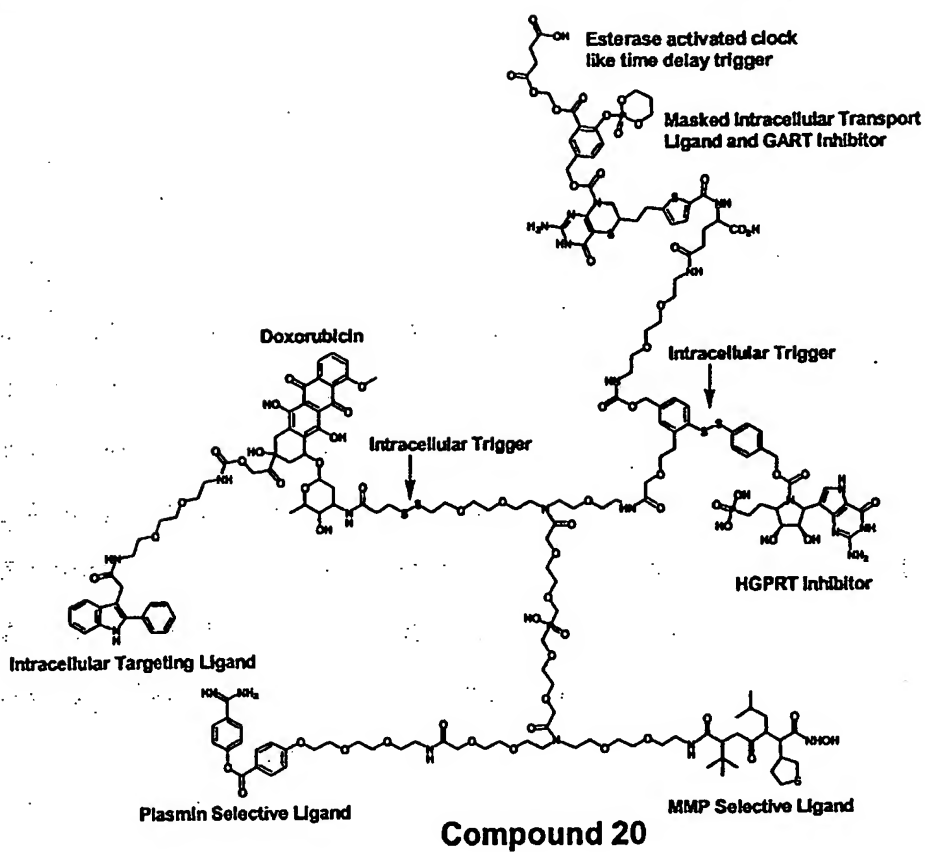
25 (3,5-dichloro-phenyl)-propionic acid 9H-fluoren-9-ylmethyl ester. Coupling with t-

Boc glycine followed by acid treatment to remove the t-Boc group will give compound 19.3.

5 Example 20

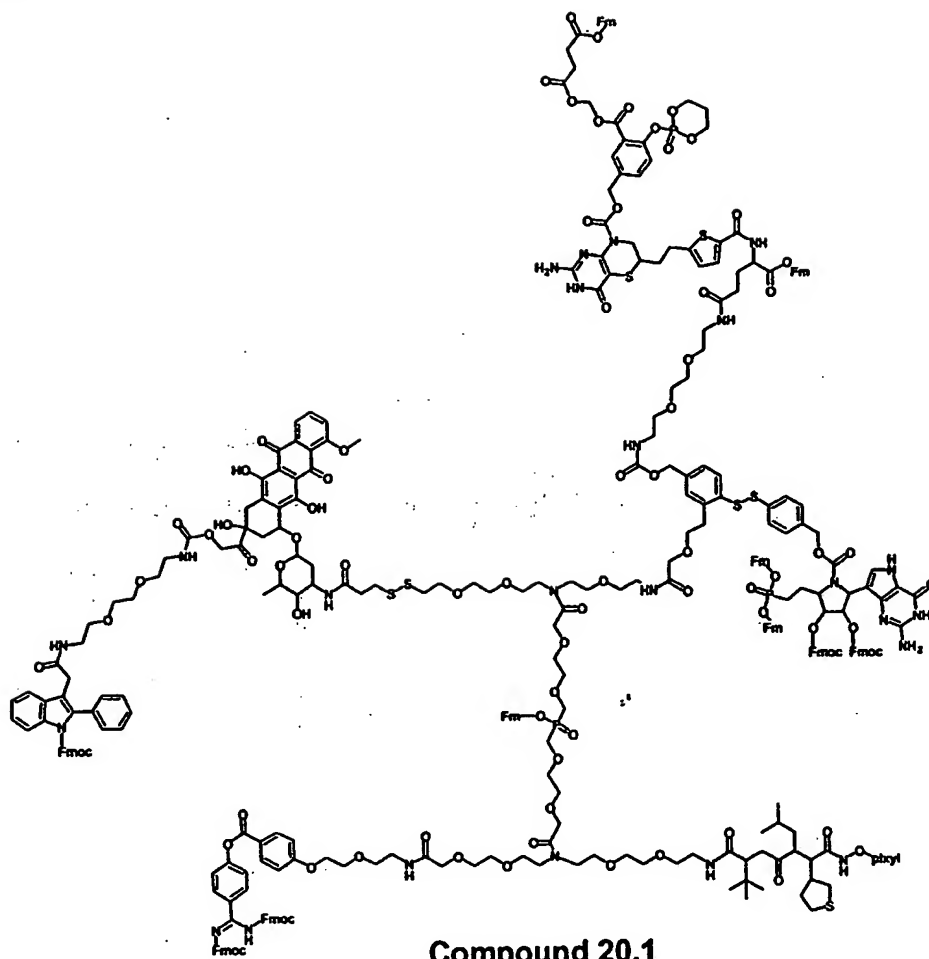
Compound 20 is a multifunctional drug delivery vehicle that will target tumors that jointly express matrilysin (or MMP's MMP1, 2, and 3) and plasmin or urokinase. The MMP ligand will bind to MMP7 with a K_i in the low nanomolar range. The plasmin ligand will acylate the active site of the serine protease
10 resulting in essentially irreversible binding. The masked intracellular transporter ligand will bind to the folate receptor after triggering by phosphatase and transport the drug into the cell. The intracellular transport ligand employed is a potent inhibitor of glycinamide ribonucleotide transformylase and will be freed, from the remainder of the drug along with an immucillinGp analog, upon
15 activation of a disulfide trigger by intracellular thioreductases. The liberated N-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethyl}-amide derivative will inhibit glycinamide ribonucleotide transformylase and inhibit denovo purine synthesis. Published crystallography data indicate that the gamma carboxylate group is exposed to solvent. Accordingly, the attached linker should not compromise inhibitor affinity.
20 The immucillinGP analog will inhibit hypoxanthene-guanine phosphoribosyltransferase and block the purine salvage pathway. The combination of inhibitors for both denovo and salvage pathways of purine metabolism should exert pronounced synergistic toxicity. The multifunctional drug delivery vehicle has a second intracellular trigger, which when activated by
25 thioreductasae, will free doxorubicin, coupled to an intracellular targeting ligand, that will bind with high affinity to the peripheral benzodiazepam receptors located

on mitochondria and impair drug efflux from the cell. Free radical processes initiated by doxorubicin, bound to the mitochondrial membranes, will damage the mitochondria resulting cytochrome release and apoptosis. Accordingly, this multifunctional delivery vehicle will provide multiple independent mechanisms of cytotoxicity. The following references relate to this subject matter: Varney M.D., et al., "Protein Structure-Based Design, Synthesis, and Biological Evaluation of 5-Thia-2,6-diamino-4(3H)-oxopyrimidines: Potent Inhibitors of Glycinamide Ribonucleotide Transformylase with Potent Cell Growth Inhibition," *J Med Chem*, 40:2502-2524 (1997); Pratt L.M., et al., "The Synthesis of Novel Matrix Metalloproteinase Inhibitors Employing the Ireland-Claisen Rearrangement," *Bioorg Med Chem Lett*, 8:1359-1364 (1998); Kozikowski A.P., et al., "Synthesis and Biology of a 7-Nitro-2,1,3-Benzoxadiazol-4-Yl Derivative of 2-Phenylindole-3-Acetamide: A Fluorescent Probe for the Peripheral-Type Benzodiazepine Receptor," *J Med Chem*, 40(16):2435-9 (1997); Shi W., et al., "The 2.0 Å Structure of Human Hypoxanthine-guanine Phosphoribosyltransferase in Complex with a Transition-state Analog Inhibitor," *Nature Structural Biology*, 6(6):588-593 (1999); 6,066,722 5/23/00 Fumeaux et al., "Inhibitors of Nucleoside Metabolism", the contents of which are incorporated herein by reference in their entirety.

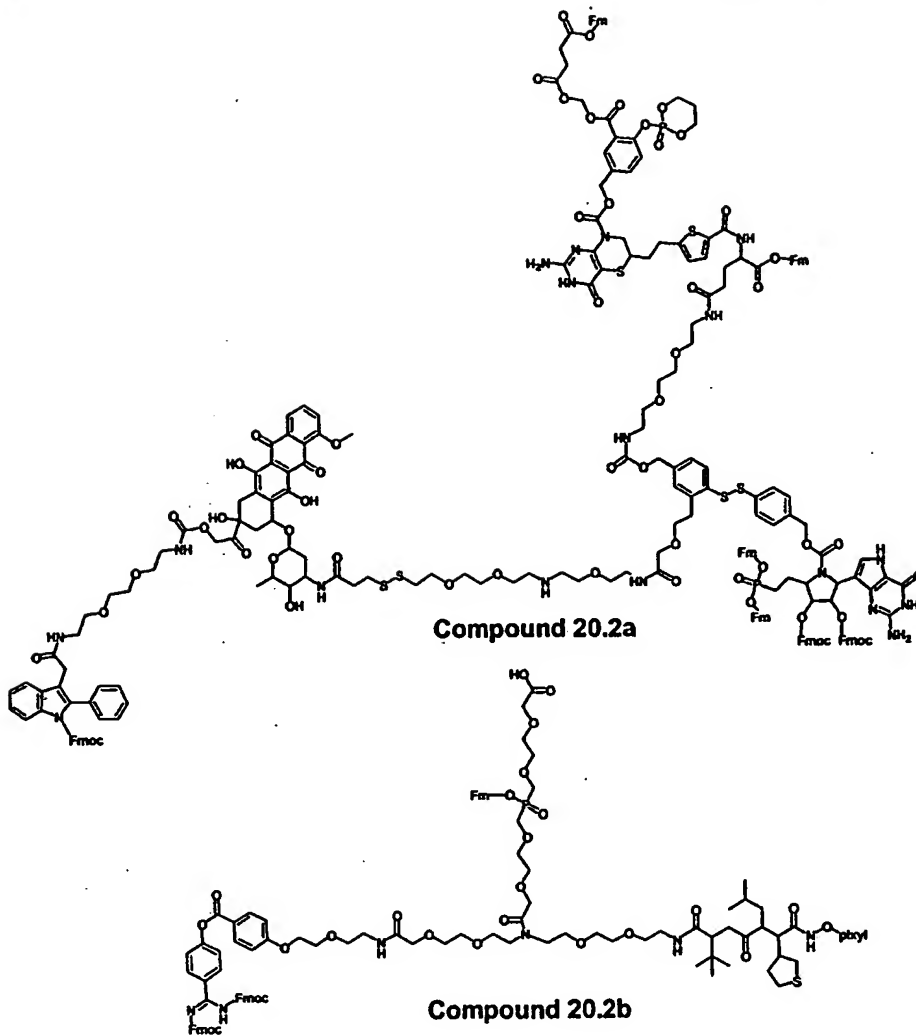


Compound 20 may be prepared by the deprotection of compound 20.1 with dilute acid to remove pixyl group followed by treatment with base to remove the

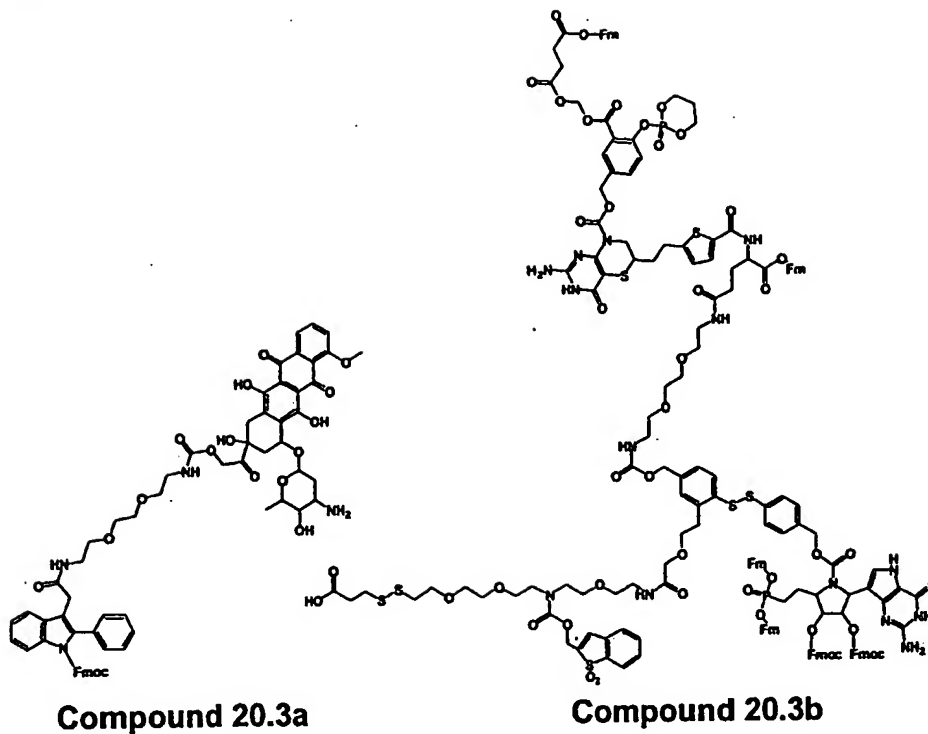
- 5 Fmoc and fluorenylmethyl ester groups.



Compound 20.1 may be prepared by coupling compound 20.2a and 20.2b.

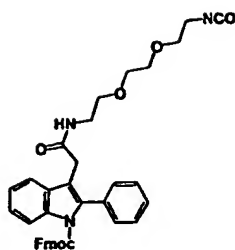


Compound 20.2a may be prepared by coupling compound 20.3a and 20.3b and then selectively removing the Bsmoc protecting group with tris(2-aminoethyl)amine under conditions that will leave the Fmoc and Fm esters intact.

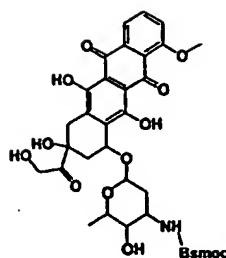


Compound 20.3a may be prepared by coupling compound 20.3a.1 and 20.3a.2

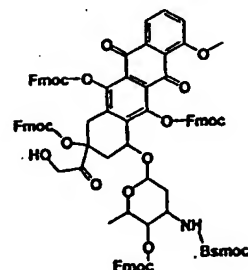
- 5 in an inert solvent in the presence of base (or a catalyst such as distannoxane) and then selectively removing the Bsmoc protecting group with tris(2-aminoethyl)amine under conditions that will leave the Fmoc group intact. The following references relate to this subject matter: Otera J., et al., "Distannoxane-Catalyzed Conversion of Chiral Alcohol to *N*-[1-(1-Naphthyl)ethyl]carbamate,"
- 10 *Synlett*, 433-434 (1995), the contents of which are incorporated herein by reference in their entirety.



Compound 20.3a.1



Compound 20.3a.2



Compound 20.3a.3

In an alternate synthetic approach, compound 20.3a.1 may be reacted with compound 20.3a.3. Compound 20.3a.3 may be prepared by treating compound 20.3a.2 with trityl chloride and base in an inert solvent and then treating the product with 9-fluorenylmethyl chloroformate in the presence of base in an inert solvent, and then treating with acid to remove the trityl group.

Compound 20.3a.1 may be prepared by coupling compound 20.4a and 2-{2-[2-(Trityl-amino)-ethoxy]-ethoxy}-ethylamine, treating with acid to remove the trityl group, and then treating the product with phosgene in an inert solvent.

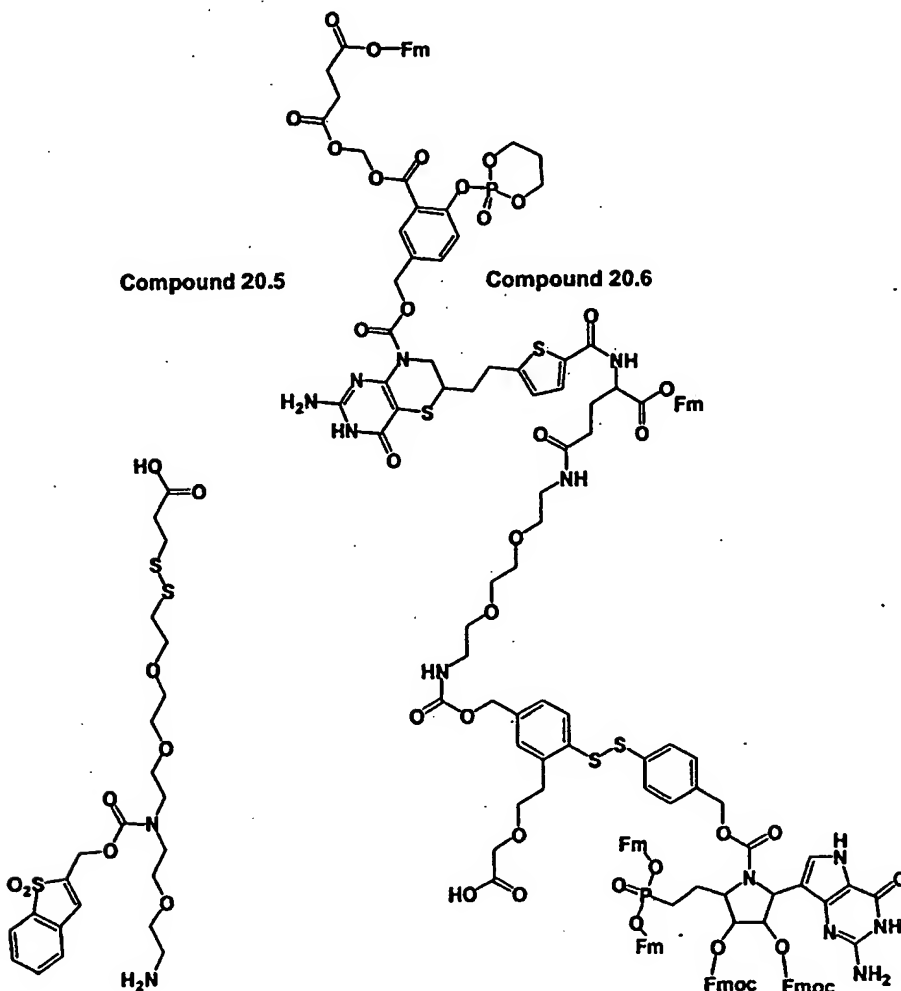
Compound 20.4a may be prepared by treatment of (2-Phenyl-1H-indol-3-yl)-acetic acid with 9-fluorenylmethyl chloroformate in the presence of base. The following references relate to this subject matter: Kozikowski A.P., et al.,
15 "Synthesis and Biology of a 7-Nitro-2,1,3-Benzoxadiazol-4-Yl Derivative of 2-Phenylindole-3-Acetamide: A Fluorescent Probe for the Peripheral-Type Benzodiazepine Receptor," *J Med Chem*, 40(16):2435-9 (1997), the contents of which are incorporated herein by reference in their entirety.



Compound 20.4a

Compound 20.3b may be prepared by converting compound 20.6 into an active ester by treatment with a reagent such as N,N', disuccinimidyl carbonate (or N-hydroxysuccinimide and dicyclohexylcarbodiimide) and then reacting with

5 compound 20.5.

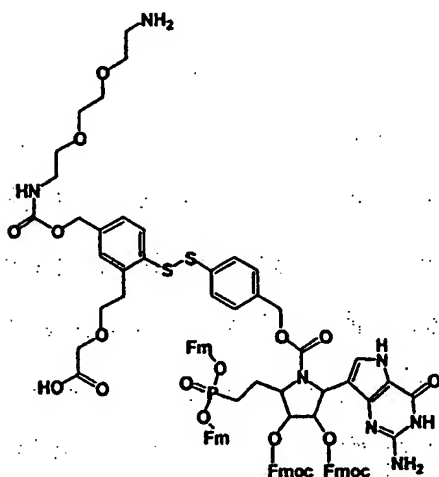


Compound 20.5 may be prepared by a multi-step procedure. [2-(2-Amino-ethoxy)-ethyl]-trityl-amine may be reacted with 2-[2-(2-Chloro-ethoxy)-ethoxy]-ethanol in an inert solvent in the presence of base and 2-[2-(2-[2-(Trityl-amino)-ethoxy]-ethylamino)-ethoxy]-ethoxy]-ethanol isolated by chromatography.

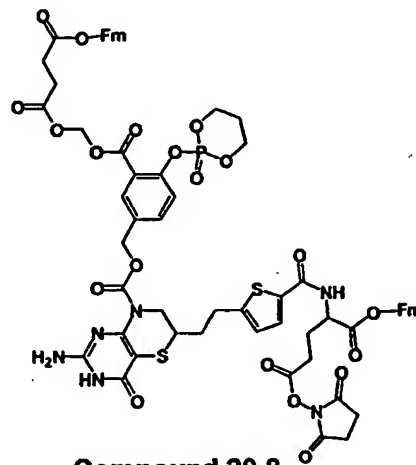
Treatment with di-*t*-butyl pyrocarbonate and in an inert solvent will give {2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethyl}-{2-[2-(trityl-amino)-ethoxy]-ethyl}-carbamic acid *tert*-butyl ester. Treatment with tosyl chloride and base will give toluene-4-sulfonic acid 2-[2-[2-(*tert*-butoxycarbonyl-{2-[2-(trityl-amino)-ethoxy]-ethyl}-amino)-ethoxy]-ethoxy]-ethyl ester. Treatment with sodium hydrogen sulfide in an inert solvent will give {2-[2-(2-Mercapto-ethoxy)-ethoxy]-ethyl}-{2-[2-(trityl-amino)-ethoxy]-ethyl}-carbamic acid *tert*-butyl ester. Then the mixed disulfide with 3-Mercapto-propionic acid 9H-fluoren-9-ylmethyl ester may then be formed by a variety of previously referenced methods. The product 3-(2-[2-[2-(*tert*-butoxycarbonyl-{2-[2-(trityl-amino)-ethoxy]-ethyl}-amino)-ethoxy]-ethoxy]-ethyldisulfanyl)-propionic acid 9H-fluoren-9-ylmethyl ester may then be treated with acid to selectively remove the trityl group and then reacted with 9-fluorenylmethyl chloroformate and base to give 3-(2-[2-[2-(*tert*-Butoxycarbonyl-{2-[2-(9H-fluoren-9-ylmethoxycarbonylamino)-ethoxy]-ethyl}-amino)-ethoxy]-ethoxy]-ethyldisulfanyl)-propionic acid 9H-fluoren-9-ylmethyl ester. Treatment with trifluoroacetic acid will remove the *t*-Boc group. Treatment with 1,1-dioxobenzo[*b*]thiophene-2-yl-methoxycarbonyl chloride and a base such as pyridine will give 3-(2-[2-[2-((1,1-dioxo-1H-116-benzo[*b*]thiophen-2-ylmethoxycarbonyl)-{2-[2-(9H-fluoren-9-yl-methoxycarbonylamino)-ethoxy]-ethyl}-amino)-ethoxy]-ethoxy]-ethyldisulfanyl)-propionic acid 9H-fluoren-9-

ylmethyl ester. Selective removal of the Fmoc group and Fm ester with a hindered base will give compound 20.5.

Compound 20.6 may be prepared by coupling compound 20.7 and 20.8.



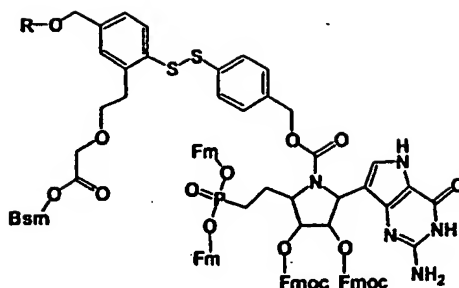
Compound 20.7



Compound 20.8

5

Compound 20.7 may be prepared by a multi-step procedure. Reacting {2-[2-(2-Amino-ethoxy)-ethoxy]-ethyl}-trityl amine and compound 20.7a, followed by
 10 treatment with acetic acid to remove the trityl group, and followed by treatment with tris(2-aminoethyl)amine to selectively cleave the Bsm ester, will give compound 20.7.



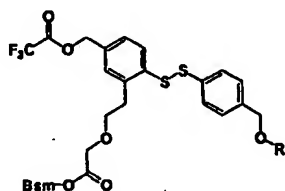
Compound 20.7a R = chlorocarbonyl

Compound 20.7b R = OH

Compound 20.7c R = CF₃CO

Compound 20.7a may be prepared by treating compound 20.7b with phosgene in an inert solvent. Compound 20.7b may be prepared by the selective removal of the trifluoroacetate group from compound 20.7c with aqueous base.

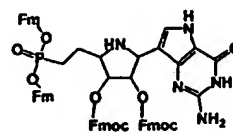
- 5 Compound 20.7c may be prepared by reacting compound 20.7d and compound 20.9 in an inert solvent in the presence of a base such as pyridine.



Compound 20.7d R = chlorocarbonyl

Compound 20.7e R = H

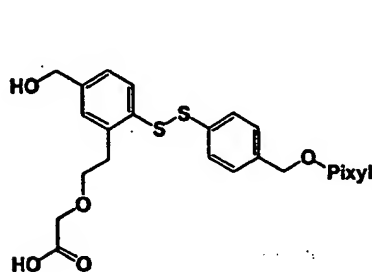
Compound 20.7f R = pixyl



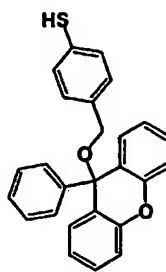
Compound 20.9

- Compound 20.7d may be prepared by treating compound 20.7e with phosgene in an inert solvent. Compound 20.7e may be prepared by treating compound 20.7f with dilute trifluoroacetic acid in an inert solvent to remove the pixyl group. Compound 20.7f may be prepared by reacting compound 20.7g with trifluoroacetic anhydride and base and then treating the product with 1,1-
- 10

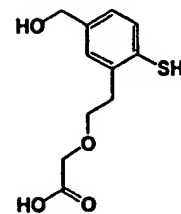
dioxobenzo[b]thiophene-2-yl-methanol and a reagent such as dicyclohexylcarbodiimide in an inert solvent.



Compound 20.7g



Compound 20.7h



Compound 20.7i

- 5 Compound 20.7g may be prepared by reacting diethyl azidocarboxylate with compound 20.7h and then reacting the product with compound 20.7i to form the mixed disulfide. The following references relate to this subject matter:

Mukaiyama T.; Takahashi K., "A Convenient Method for the Preparation of Unsymmetrical Disulfides by the use of Diethyl Azodicarboxylate," *Tetrahedron*

- 10 *Letters*, 56:5907-5908 (1968), the contents of which are incorporated herein by reference in their entirety.

- Compound 20.7h may be prepared by reacting 2 equivalents of 9-chloro-9-phenyl-9H-xanthene (pixyl chloride) with 4-mercapto phenol disulfide and base
15 and then reducing the disulfide with an agent such as sodium borohydride.

- Compound 20.7i may be prepared by a multi-step procedure. A Friedel-Crafts reaction between 4-mercapto-benzoic acid and chlorocarbonylmethoxy-acetic acid methyl ester will give 4-mercapto-3-(2-methoxycarbonylmethoxy-acetyl)-
20 benzoic acid. Reduction of the ketone with Zn/HCL will give 4-mercapto-3-(2-methoxycarbonylmethoxy-ethyl)-benzoic acid. Treatment with borane in a

solvent such as tetrahydrofuran will reduce the carboxylic acid to the alcohol.

Hydrolysis of the methyl ester will give compound 20.7i. The following

references relate to this subject matter: Gore P.H., "Aromatic Ketone Synthesis, in " *Friedel-Crafts and Related Reactions*, Olah G.A. (edt.), John Wiley & Sons,

5 p.55 (1964); Read R.R.; Wood J. Jr., "o-n-Heptylphenol," *Org Syn Coll Volume 3*,

pp. 444-446; Yoon N.M.; Pak C.S., "Selective Reductions. XIX. The Rapid

Reaction of Carboxylic Acids with Borane-Tetrahydrofuran. A Remarkable

Convenient Procedure for the Selective Conversion of Carboxylic Acids to the

Corresponding Alcohols in the Presence of Other Functional Groups," *J Org*

10 *Chem*, 33(16):2786-2792 (1973), the contents of which are incorporated herein

by reference in their entirety.

Compound 20.9 may be prepared by a multi-step method. Compound 20.9.1 is

a known compound. The following references relate to this subject matter:

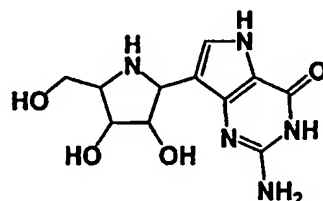
6,066,722 5/23/00 Fumeaux et al., "Inhibitors of Nucleoside

15 Metabolism". Shi W., et al., "The 2.0 Å Structure of Human Hypoxanthine-

guanine Phosphoribosyltransferase in Complex with a Transition-state Analog

Inhibitor," *Nature Structural Biology*, 6(6):588-593 (1999), the contents of which

are incorporated herein by reference in their entirety.



Compound 20.9.1

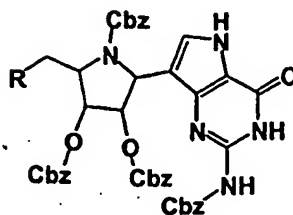
20

Treatment of compound 20.9.1 with trityl chloride to protect the 5' hydroxy group,

followed by treatment with benzyloxycarbonyl chloride (Cbz chloride) in an inert

solvent, in the presence of a base, such as pyridine base will give compound

20.9.2a.



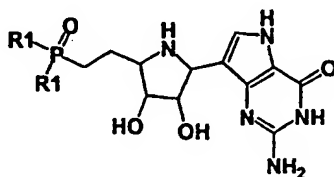
Compound 20.9.2a R = O-trityl

Compound 20.9.2b R = OH

Compound 20.9.2c R = O=

Treatment with acid will remove the trityl group and give compound 20.9.2b.

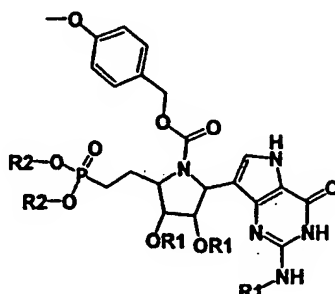
- 5 Oxidation with dimethylsulfoxide and an agent such as dicyclohexylcarbodiimide will give the aldehyde (compound 20.9.2c). Reaction with [diisopropyl]-methylidene] triphenylphosphorane followed by catalytic hydrogenation with palladium on carbon will give compound 20.10a. The following references relate to this subject matter: Xu Y., et al., "Preparation of New Wittig Reagents and
- 10 Their Application to the Synthesis of $\alpha\beta$ -Unsaturated Phosphonates," *J Org Chem*, 61:7697-7701 (1996); Montgomery J.A.; Thomas H.J., "Phosphonate Analogue of 2'-Deoxy-5-fluorouridylic Acid," *J Med Chem*, 22(1):109-111 (1979), the contents of which are incorporated herein by reference in their entirety.



Compound 20.10a R1 = isopropoxy

Compound 20.10b R1 = OH

Treatment of compound 20.10a with hydrochloric acid will give compound 20.10b as the hydrochloride salt. Treatment with 2-(4-methoxybenzyloxycarbonyloxyimino)-2-phenyl acetonitrile and base will give compound 20.10c.



Compound 20.10c R1= OH R2 = H

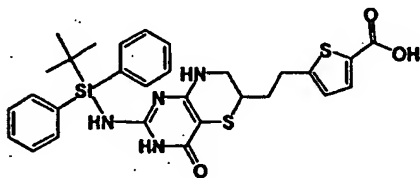
Compound 20.10d R1= Fmoc R2 = H

Compound 20.10e R1= Fmoc R2 = Fm

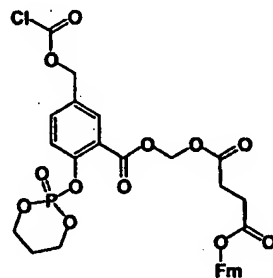
- 5 Treatment of compound 20.10c with 9-fluorenylmethyl chloroformate and base in an inert solvent will give compound 20.10.d. Compound 20.10d may be converted into the bis 9-fluorenylmethyl ester by treatment with (9H-Fluoren-9-yl)-methanol and a condensing reagent such as 1-mesitylenesulphonyl chloride. Alternatively, compound 20.10d may be converted into the dichlorophosphonate
- 10 derivative by reagents such as oxalyl chloride/dimethylformamide and reacted with (9H-Fluoren-9-yl)-methanol and base to give compound 20.10e. Treatment of compound 20.10e with acid will remove the p-methoxybenzyloxycarbonyl protecting group and will give compound 20.9.
- 15 Compound 20.8 may be prepared by a multi-step process. The following references relate to this subject matter: Varney M.D., et al., "Protein Structure-Based Design, Synthesis, and Biological Evaluation of 5-Thia-2,6-diamino-4(3H)-oxypyrimidines: Potent Inhibitors of Glycinamide Ribonucleotide Transformylase

with Potent Cell Growth Inhibition," *J Med Chem*, 40:2502-2524 (1997), the contents of which are incorporated herein by reference in their entirety.

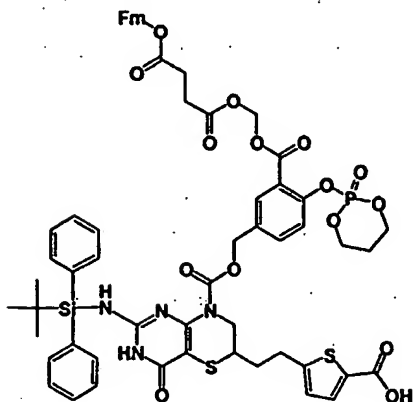
Treatment of compound 20.8.1 with compound 20.8.2 in the presence of base in
5 an inert solvent will give compound 20.8.3.



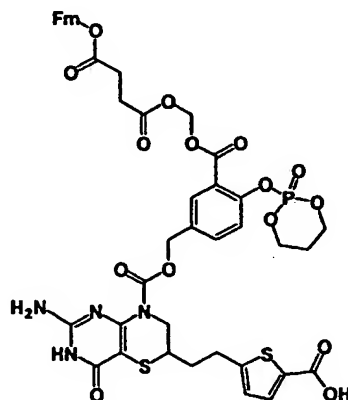
Compound 20.8.1



Compound 20.8.2

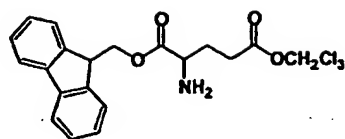
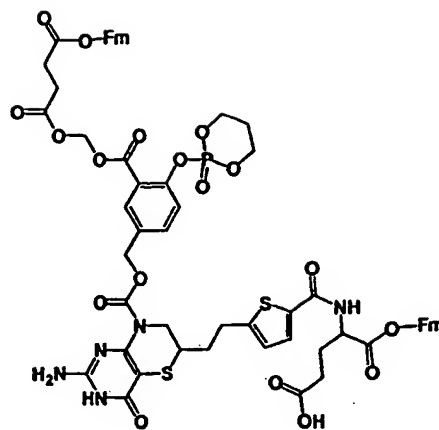


Compound 20.8.3



Compound 20.8.3b

The silyl based protecting group may be removed with a reagent such as pyridine- HF to give compound 20.8.3b. Compound 20.8.3b may be coupled with compound 20.8.3c and the trichloroethyl ester cleaved with Zn and acid to
10 give compound 20.8.3d.

**Compound 20.8.3c****Compound 20.8.3d**

Treating compound 20.8.3d with dicyclohexylcarbodiimide and N-hydroxy-succinimide in an inert solvent will give compound 20.8.

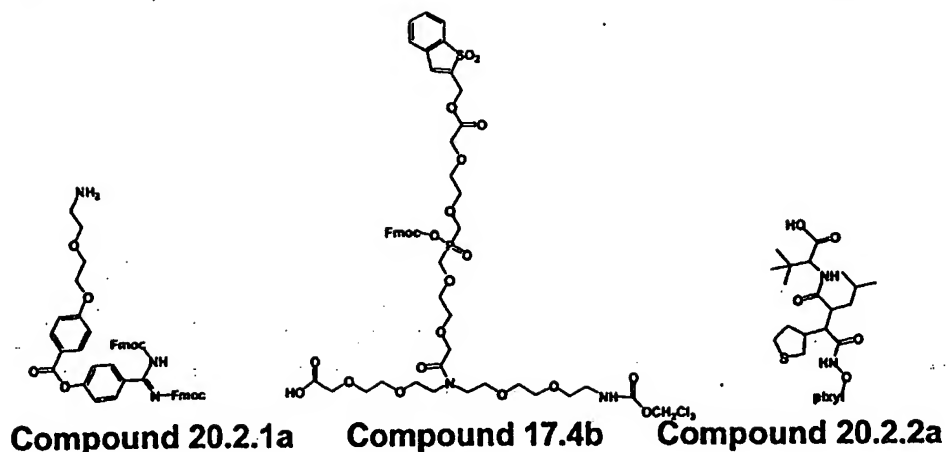
5

Compound 20.8.3c may be prepared by a multi-step process. The known compound L- N-t-Boc glutamic acid α (9H-Fluoren-9-yl)-methyl ester may be coupled with 2,2,2, trichloroethanol with a reagent such as dicyclohexylcarbodiimide in an inert solvent. Treatment with acid will remove the

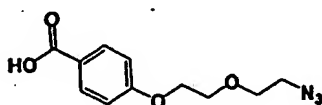
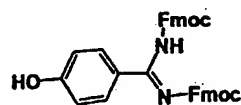
10 t-Boc group and give compound 20.8.3c as the salt.

Compound 20.2b may be prepared by a multi-step process. Coupling compound 20.2.1a and compound 17.4b, followed by removal of the trichloroethylcarbonyl protecting group with Zn and acid, followed by coupling compound 20.2.2a,

15 followed by selective removal of the Bsmoc group with tris(2-aminoethyl)-amine will give compound 20.2b.



- Compound 20.2.1a may be prepared by coupling compound 20.2.1b and 20.2.1c and then reducing the azido group to an amino group. The reduction of the azido group may be carried out by a variety of methods including catalytic hydrogenation with palladium on carbon, or triphenyl phosphine water.

**Compound 20.2.1b****Compound 20.2.1c**

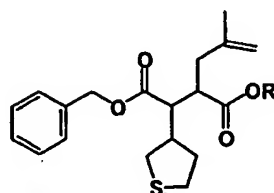
- Compound 20.2.1b may be prepared by a multi-step process. Reacting 2-(2-Chloro-ethoxy)-ethanol and 4-Hydroxy-benzoic acid tert-butyl ester in the presence of base in an inert solvent will give 4-[2-(2-Hydroxy-ethoxy)-ethoxy]-benzoic acid tert-butyl ester. Treatment with tosyl chloride and base followed by the reaction with lithium azide will give 4-[2-(2-azido-ethoxy)-ethoxy]-benzoic acid tert-butyl ester. The tert-butyl ester may then be cleaved with acid to give compound 20.2.1b.

Compound 20.2.1c may be prepared by treating 4-hydroxy-benzamidine with a silylating agent such as chlorotrimethylsilane and base or hexamethyldisilazane and then treating with 9-fluorenylmethyl chloroformate and base, and hydrolyzing the trimethylsilyl ether group.

5

Compound 20.2.2a may be prepared by a multi-step procedure. The known compound 20.2.2b may be converted into the methyl ester compound 20.2.2c by routine methods. The following references relate to this subject matter: Pratt L.M., et al., "The Synthesis of Novel Matrix Metalloproteinase Inhibitors

10 Employing the Ireland-Claisen Rearrangement," *Bioorg Med Chem Lett*, 8:1359-1364 (1998), the contents of which are incorporated herein by reference in their entirety.



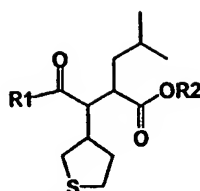
Compound 20.2.2b R₁ = H

Compound 20.2.2c R₁ = methyl

Catalytic hydrogenation with palladium on carbon will give compound 20.2.2d.

15 Using routine methods the t-butyl ester compound 20.2.2e may be prepared.

Selective hydrolysis of the methyl ester with aqueous sodium hydroxide will give compound 20.2.2f.

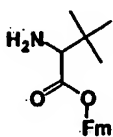


Compound 20.2.2d R1 = OH R2 = methyl

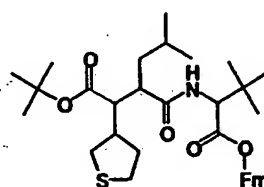
Compound 20.2.2e R1 = t-butoxy R2 = methyl

Compound 20.2.2f R1 = t-butoxy R2 = H

Coupling with compound 20.2.2f and compound 20.2.2g will give compound 20.2.2h.



Compound 20.2.2g

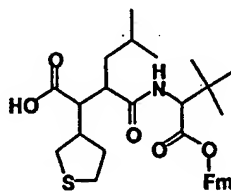


Compound 20.2.2h

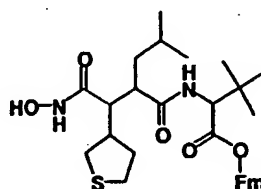
5

Treatment with acid will cleave the t-butyl ester and give compound 20.2.2i.

Coupling with O-trimethylsilyl hydroxylamine and an agent such as dicyclohexylcarbodiimide will give, after hydrolysis, compound 20.2.2j.



Compound 20.2.2i



Compound 20.2.2j

10

Treatment with 9-chloro-9-phenyl-9H-xanthene and base will give compound 20.2.2a.

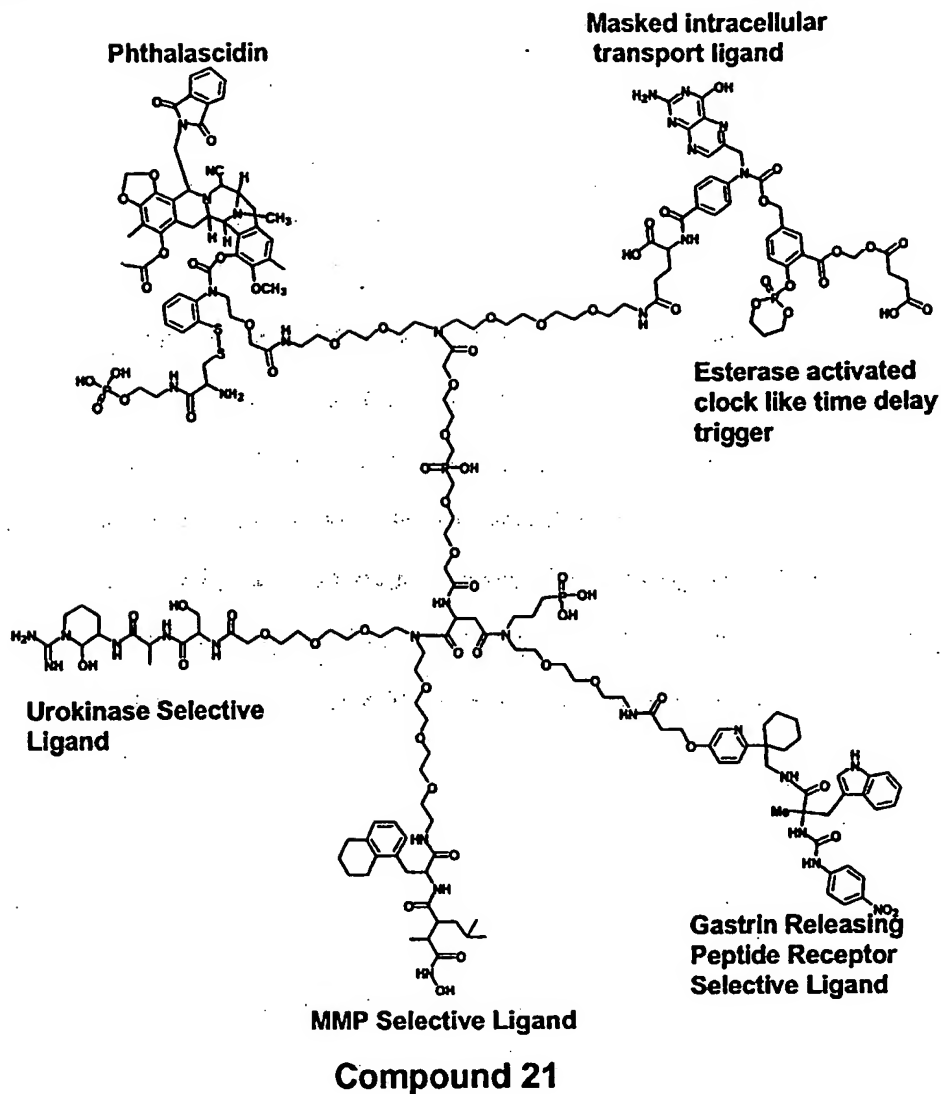
Example 21

Compound 21 is a multifunctional drug delivery vehicle that is targeted against tumor cells that express urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1) and gastrin releasing peptide receptor. Individually each ligand will

5 bind at nanomolar concentrations to its receptor. Accordingly, binding of any two of the ligands should give essentially irreversible binding to the tumor cell. The drug has a masked folic acid group as an intracellular transport ligand. The drug will release Phthalascidin a cytotoxin that has an IC_{50} in the 0.1-1 nM range. The phthalascidin is linked to the drug complex by a carbamate group that will

10 undergo cleavage upon reduction of a disulfide bond. The following references relate to this subject matter: Martinez EJ, et al., "Phthalascidin, A Synthetic Antitumor Agent with Potency and Mode of Action Comparable to Ecteinascidin 743," *Proc Natl Acad Sci USA*, 96:3496-3501 (1999); Ashwood V., et al., "PD 176252—The First High Affinity Non-Peptide Gastrin-Releasing Peptide (BB2)

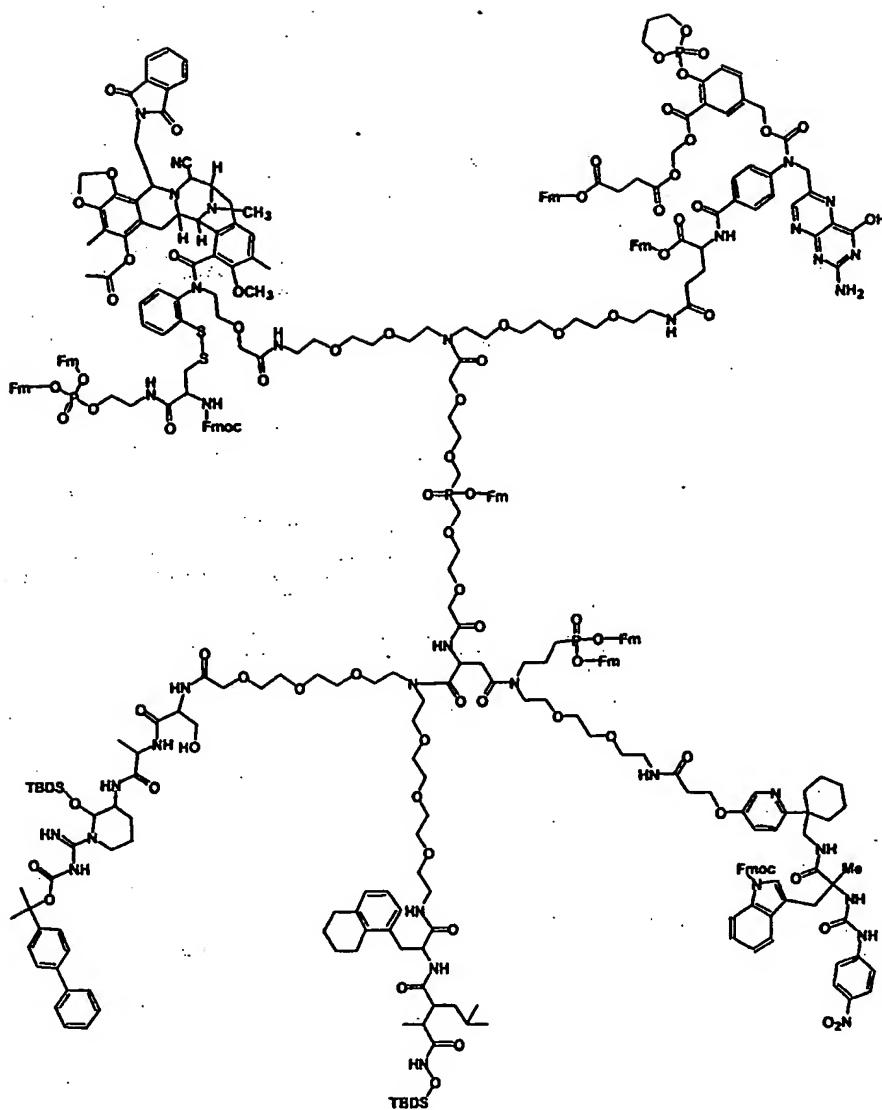
15 Receptor Antagonist," *Bioorg Med Chem Lett*, 8(18):2589-94 (1998); WO 98/07718 2/26/98 Horwell et al., "Non-Peptide Bombesin Receptor Antagonist", the contents of which are incorporated herein by reference in their entirety.



Compound 21 may be prepared by deprotecting compound 21a with

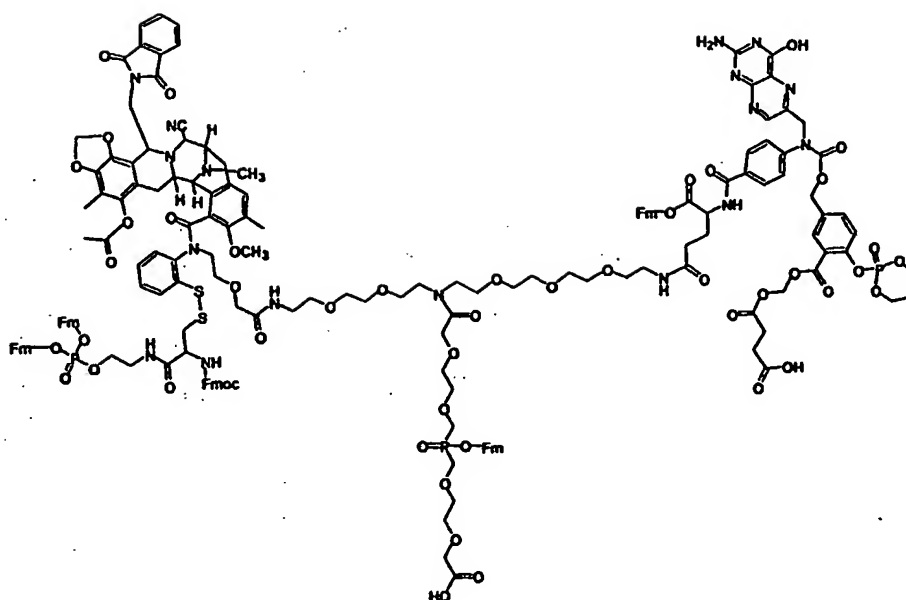
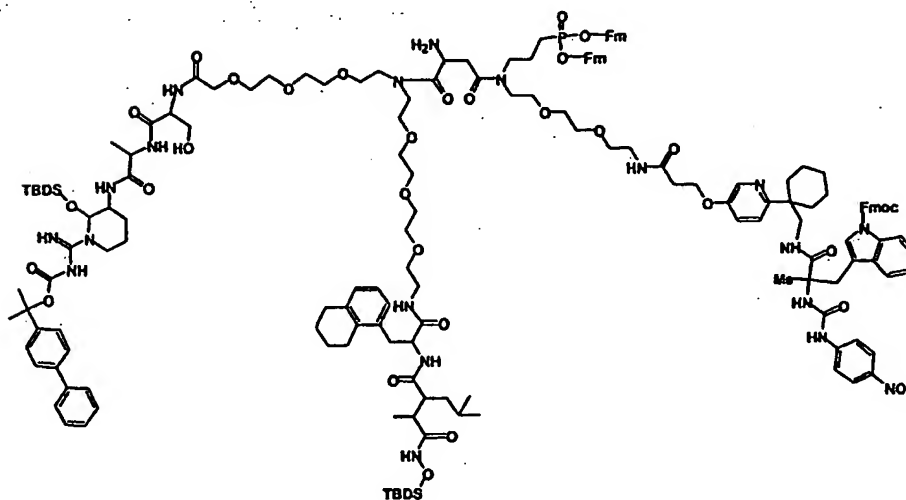
- 5 tetrabutylammonium fluoride to remove both the silyl and fluorenyl based protecting groups. A deblocking step with dilute acid is also required.

Alternatively, a variety of other reagents known to cleave t-butyldimethylsilyl ethers may be employed. The Fmoc and fluorenylmethyl esters may be cleaved with base.



Compound 21a

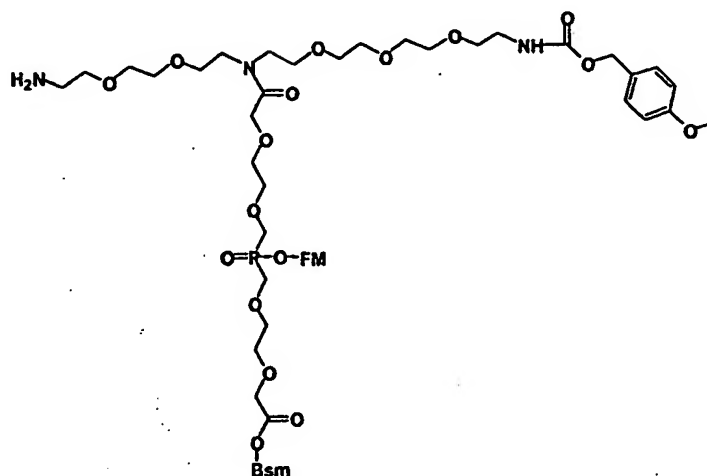
Compound 21a may be prepared by coupling compound 21.1 and compound 21.2.

**Compound 21.1****Compound 21.2**

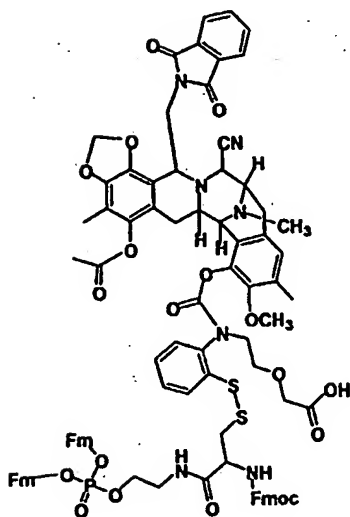
Compound 21.1 may be prepared by a multi-step process. Coupling compounds

- 5 21.1.1 and 21.1.2, followed by removal of the p-methoxy-benzyloxycarbonyl protecting group with dilute trifluoroacetic acid in an inert solvent, followed by

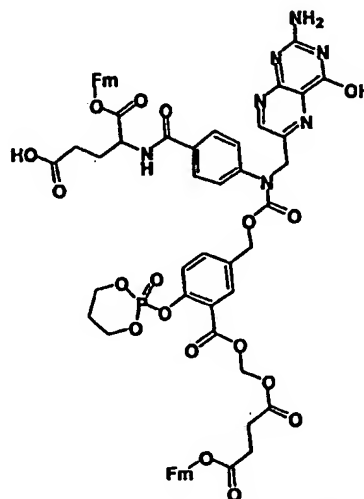
coupling with compound 6.2.0b, followed by selective cleavage of the Bsm group with tris(2-aminoethyl)-amine will give compound 21.1.



Compound 21.1.1



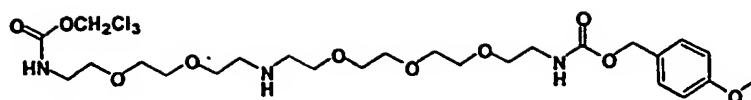
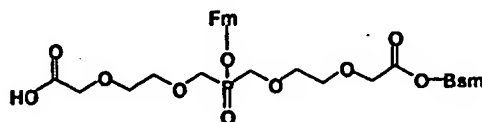
Compound 21.1.2



Compound 6.2.0b

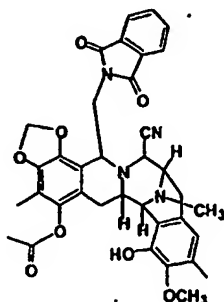
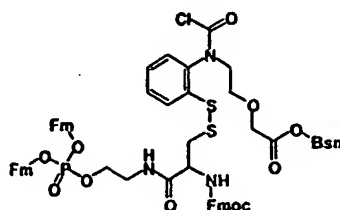
Compound 21.1.1 may be prepared by coupling compounds 21.1.1a and 21.1.1b

- 5 and then removing the trichloroethoxycarbonyl group with Zn and phosphate buffer or Zn and dilute acid.

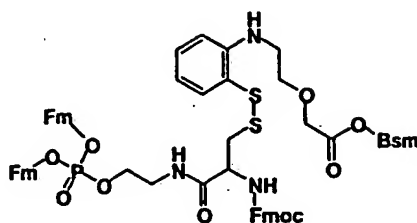
**Compound 21.1.1a****Compound 21.1.1b**

The synthesis of compound 21.1.1b was described previously. Compound 21.1.1a may be prepared by a multistep procedure. 2-[2-(2-Amino-ethoxy)-ethoxy]-ethanol may be treated with 2,2,2-trichloroethylchloroformate and base to give {2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethyl}-carbamic acid 2,2,2-trichloro-ethyl ester. Treatment with tosyl chloride and base will give toluene-4-sulfonic acid 2-[2-[2-(2,2,2-trichloro-ethoxycarbonylamino)-ethoxy]-ethoxy]-ethyl ester. Reaction with (2-[2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy]-ethyl)-carbamic acid 4-methoxy-benzyl ester and base in an inert solvent will give, after purification, compound 21.1.1a.

Compound 21.1.2 may be prepared by reacting compounds 21.1.2a and Phthalascidin in an inert solvent in the presence of a base such as pyridine.

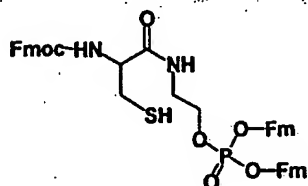
**Phthalascidin****Compound 21.1.2a**

Compound 21.1.2a may be prepared by treating compound 21.1.2b with phosgene in an inert solvent.

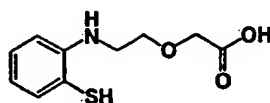


Compound 21.1.2b

- 5 Compound 21.1.2b may be prepared by a multistep process. Reacting diethyl azidocarboxylate with compound 14.11.4 and then reacting the product with compound 17.11.1a will form the mixed disulfide.



Compound 14.11.4



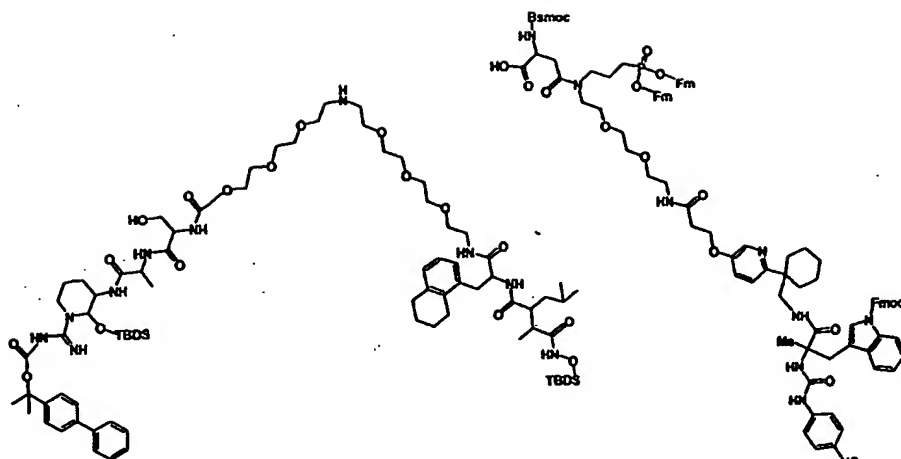
Compound 17.11.1a

10

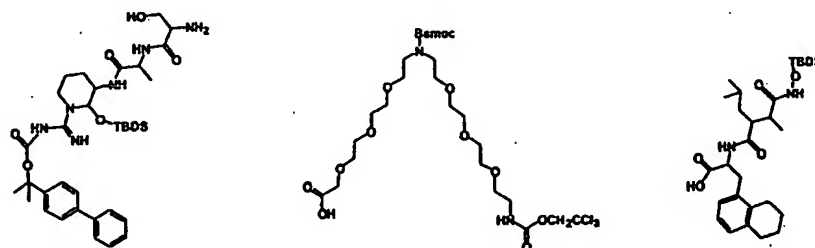
The product may then be treated with di-*t*-butyl pyrocarbonate in an inert solvent. Treating with (1,1-Dioxo-1H-1λ6-benzo[b]thiophen-2-yl)-methanol and dicyclohexylcarbodiimide in an inert solvent, followed by acid treatment to remove the *t*-Boc group will give compound 21.1.2b.

15

Compound 21.2 may be prepared by coupling compounds 21.2.1a and 21.2.2a and then treating with tris(2-aminoethyl)-amine to selectively cleave the Bsmoc group.

**Compound 21.2.1a****Compound 21.2.2a**

Compound 21.2.1a may be prepared by a multi-step process. Compound
 5 21.2.1b and 21.2.1c may be coupled and then the product may be treated with
 Zn phosphate buffer to remove the trichloroethoxycarbonyl protecting group.
 Coupling with compound 21.2.1d followed by the removal of the Bsmoc group
 with tris(2-aminoethyl)-amine will give compound 21.2.1a.

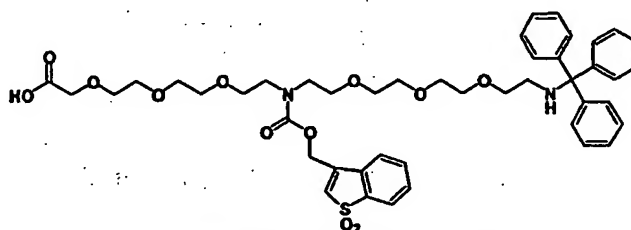
**Compound 21.2.1b Compound 21.2.1c Compound 21.2.1d**

10

The synthesis of compound 21.2.1b was given previously as compound 14.7.

Compound 21.2.1c may be prepared by a multi-step process. 2-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-ethylamine may be treated with trityl chloride and base and (2-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-ethyl)-trityl-amine isolated.

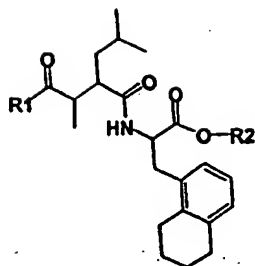
- Alkylation with {2-[2-(2-Chloro-ethoxy)-ethoxy]-ethoxy}-acetic acid in an inert solvent in the presence of base will give [2-(2-[2-[2-(2-{2-[2-(trityl-amino)-ethoxy]-ethoxy)-ethoxy]-ethylamino]-ethoxy]-ethoxy)-ethoxy]-acetic acid. Treating with (1,1-Dioxo-1H-1λ6-benzo[b]thiophen-2-yl)-methyl chloroformate and base in an inert solvent will give compound 21.2.1c.2.



Compound 21.2.1c.2

- Treating with acid to remove the trityl group followed by the reaction with 2,2,2 trichloroethyl chloroformate and base in an inert solvent or under Schotten-Bauman conditions will give compound 21.2.1c.

- Compound 21.2.1d may be prepared by a multi-step procedure from compound 14.6.5. Coupling of compound 14.6.5 with 2,2,2 trichloroethanol will give compound 21.2.1d.1. Treatment with acid will cleave the t-butyl ester and give compound 21.2.1d.2. Treatment with (9H-Fluoren-9-yl)-methanol and a coupling agent such as dicyclohexylcarbodiimide will give compound 21.2.2d.3. Treatment with Zn and acid will cleave the trichloroethyl ester and give compound 21.2.1d.4. Coupling with O-tert-butyl-dimethyl-silyl hydroxylamine will give compound 21.2.1d.5. Treatment with base will cleave the fluorenylmethyl ester and give compound 21.2.1d.

**Compound 14.6.5**

R1 = OH R2 = t-butyl

Compound 21.2.1d.1R1 = OCH₂CCl₃ R2 = t-butyl**Compound 21.2.1d.2**R1 = OCH₂CCl₃ R2 = H**Compound 21.2.1d.3**R1 = OCH₂CCl₃ R2 = 9-H-fluorenyl-methyl**Compound 21.2.1d.4**

R1 = OH R2 = 9-H-fluorenyl-methyl

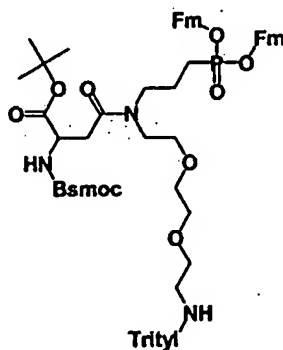
Compound 21.2.1d.5

R1 = -NHO-t-butyl(dimethylsilyl) R2 = 9-H-fluorenyl-methyl

Compound 21.2.2a may be prepared by a multi-step process.

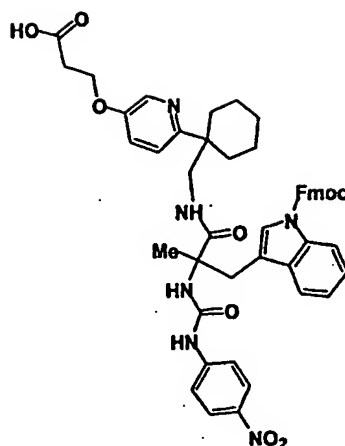
5

Compound 13b3 may be coupled with Bsmoc – L– aspartic acid α t-butyl ester in an inert solvent will give compound 21.2.2c.

**Compound 21.2.2c**

Treating with acid will remove the trityl group. The product may be coupled to

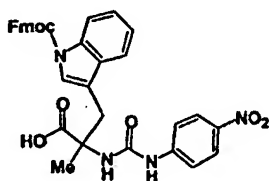
10 compound 21.2.2e. Treatment with acid will cleave the t-Butyl ester group and give compound 21.2.2a.



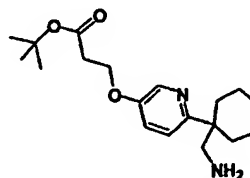
Compound 21.2.2e

Compound 21.2.2e may be prepared by coupling compound 21.2.2f and compound 21.2.2g and treating with acid to cleave the t-butyl ester. The following reference relates to this subject matter: WO 98/07718, 2/26/98,

- 5 Horwell et al., "Non-Peptide Bombesin Receptor Antagonist", the contents of which are incorporated herein by reference in their entirety.



Compound 21.2.2f



Compound 21.2.2g

- 10 Compound 21.2.2g may be prepared by a multi-step process. 6-Methyl-pyridin-3-ol may be alkylated with 3-Bromo-propionic acid tert-butyl ester in an inert solvent in the presence of a strong base such as sodium hydride to give 3-(6-Methyl-pyridin-3-yloxy)-propionic acid tert-butyl ester. This can be oxidized with m-chloroperbenzoic acid to the corresponding N-oxide, which on reflux in acetic

anhydride will rearrange to give 3-(6-Acetoxymethyl-pyridin-3-yloxy)-propionic acid tert-butyl ester. Treatment with sodium hydroxide will give 3-(6-Hydroxymethyl-pyridin-3-yloxy)-propionic acid tert-butyl ester. Treatment with tosyl chloride and base in an inert solvent followed by treatment with potassium cyanide will give 3-(6-cyanomethyl-pyridin-3-yloxy)-propionic acid tert-butyl ester. Alkylation with 1,5-dibromo-pentane, in the presence of a strong base such as sodium hydride, in an inert solvent will give 3-[6-(1-Cyano-cyclohexyl)-pyridin-3-yloxy]-propionic acid tert-butyl ester. Catalytic hydrogenation will give 3-[6-(1-aminomethyl-cyclohexyl)-pyridin-3-yloxy]-propionic acid tert-butyl ester

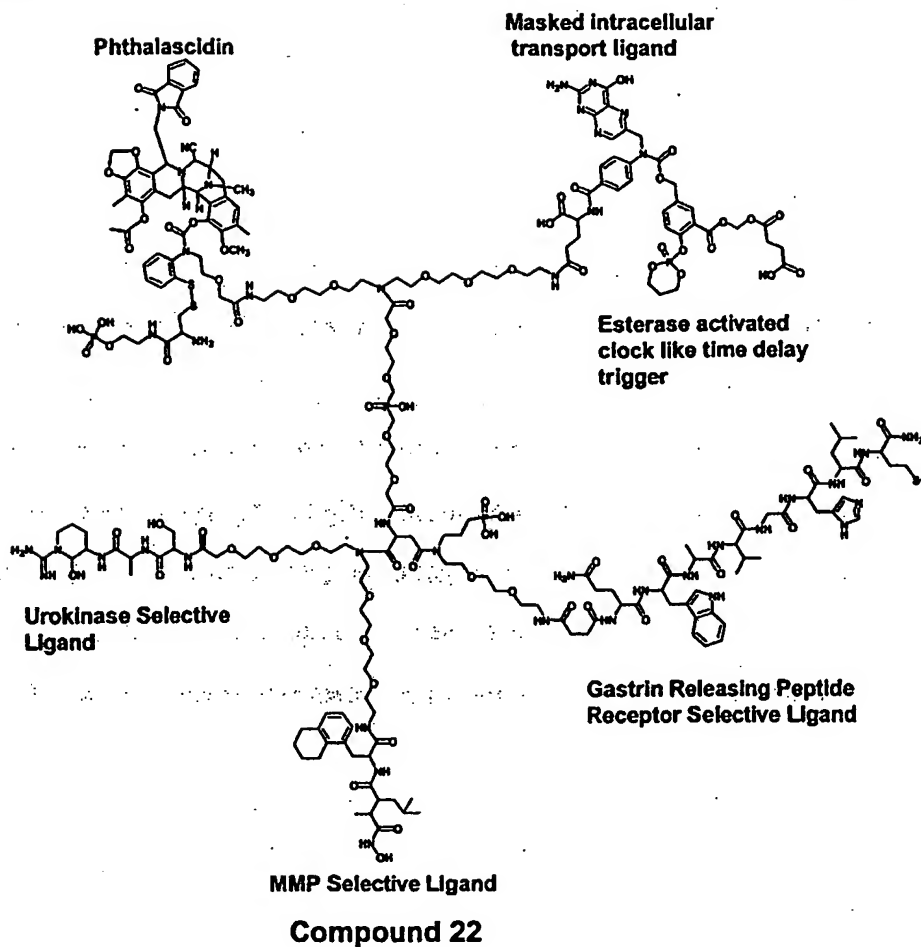
10 (compound 21.2.2g). The following references relate to this subject matter: WO 98/07718, 2/26/98 Horwell et al., "Non-Peptide Bombesin Receptor Antagonist", the contents of which are incorporated herein by reference in their entirety.

15

Example 22

Compound 22 is similar to compound 21, however a different gastrin releasing protein receptor selective ligand is employed. The following references relate to this subject matter: Karra S. R., et al., ^{99m}Tc-Labeling and in Vivo Studies of a Bombesin Analogue with a Novel Water-Soluble Dithiadiphosphine-Based Bifunctional Chelating Agent," *Bioconjugate Chem*, 10(2):254-260 (1999), the contents of which are incorporated herein by reference in their entirety.

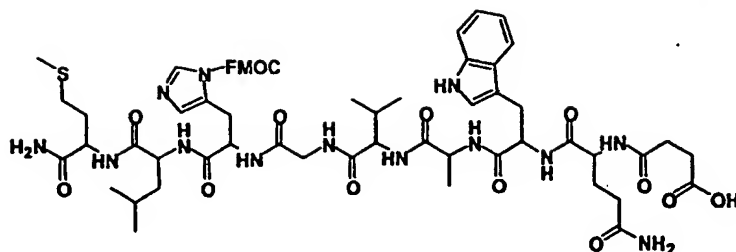
20



Compound 22 may be prepared by replacing compound 21.2.2e with compound

5 22.1 in the process described for the synthesis of compound 21.

Compound 22.1 may be prepared using routine methods of peptide synthesis.



Compound 22.1

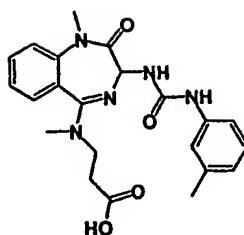
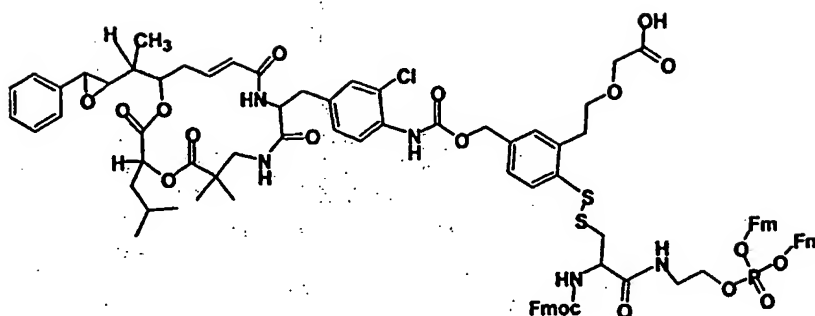
Example 23

Compound 23 is a multifunctional drug delivery vehicle with targeting ligands for urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1) and Gastrin/Cholecystokinin type B Receptors. The drug has a masked folic acid group as an intracellular transport ligand that will be activated by esterase. A derivative of cryptophycin that is toxic at picomolar concentrations will be freed upon cleavage of a disulfide trigger by thiol reductases. The following references relate to this subject matter: Showell G.A., et al., "High-Affinity and Potent, Water-Soluble 5-Amino-1,4-Benzodiazepine CCKB/Gastrin Receptor Antagonists Containing a Cationic Solubilizing Group," *J Med Chem*, 37(6):719-21 (1994); Panda D., et al., "Antiproliferative Mechanism of Action of Cryptophycin-52: Kinetic Stabilization of Microtubule Dynamics by High-Affinity Binding to Microtubule Ends," *Proc Natl Acad Sci USA*, 95:9313-9318 (1998); Smith C.D., et al., "Cryptophycin: A New Antimicrotubule Agent Active against Drug-resistant Cells," *Cancer Res*, 54:3779-3784 (1994); Patel V.F., et al., "Novel Cryptophycin Antitumor Agents: Synthesis and Cytotoxicity of Fragment "B" Analogues," *J Med Chem*, 42:2588-2603 (1999), the contents of which are incorporated herein by reference in their entirety.

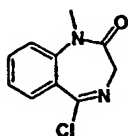
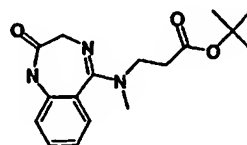
Cryptophycin Analog**Masked intracellular
transport ligand****Esterase activated
clock like time delay
trigger****Urokinase Selective
Ligand****CCK_B / Gastrin Receptor
Selective Ligand****MMP Selective Ligand****Compound 23**

Compound 23 may be prepared by replacing compound 21.2.2e with compound

- 5 23.1 and replacing compound 21.1.2 with compound 23.2 as in the process
described for the synthesis of compound 21.

**Compound 23.1****Compound 23.2**

- 5 Compound 23.1 may be prepared by the methods described by Showell G. A. The following references relate to this subject matter: Showell G.A., et al., "High-Affinity and Potent, Water-Soluble 5-Amino-1,4-Benzodiazepine CCKB/Gastrin Receptor Antagonists Containing a Cationic Solubilizing Group," *J Med Chem*, 37(6):719-21 (1994), the contents of which are incorporated herein by reference
- 10 in their entirety.

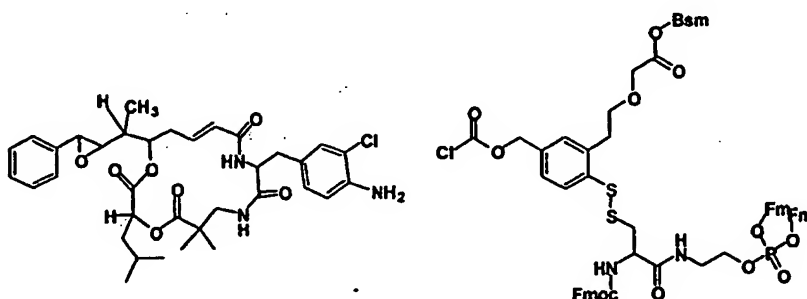
**Compound 23.1a****Compound 23.1b**

Treating compound 23.1a with 3-methylamino-propionic acid tert-butyl ester and a base such as triethylamine in an inert solvent will give compound 23.1b.

Compound 21.3b may then be transformed into the t-butyl ester of compound 23.1 using the methods described by Showell G. A et al. Treatment with acid will

5 cleave the t-butyl ester and give compound 23.1.

Compound 23.2 may be prepared by reacting 23.2a and 23.2b in an inert solvent in the presence of a base such as pyridine and then treating with tris(2-aminoethyl)-amine to selectively cleave the Bsm ester.



Compound 23.2a

Compound 23.2b

10

Compound 23.2a is a known compound. The following references relate to this subject matter: Patel V.F., et al., "Novel Cryptophycin Antitumor Agents: Synthesis and Cytotoxicity of Fragment "B" Analogues," *J Med Chem*, 42:2588-2603 (1999), the contents of which are incorporated herein by reference in their

15

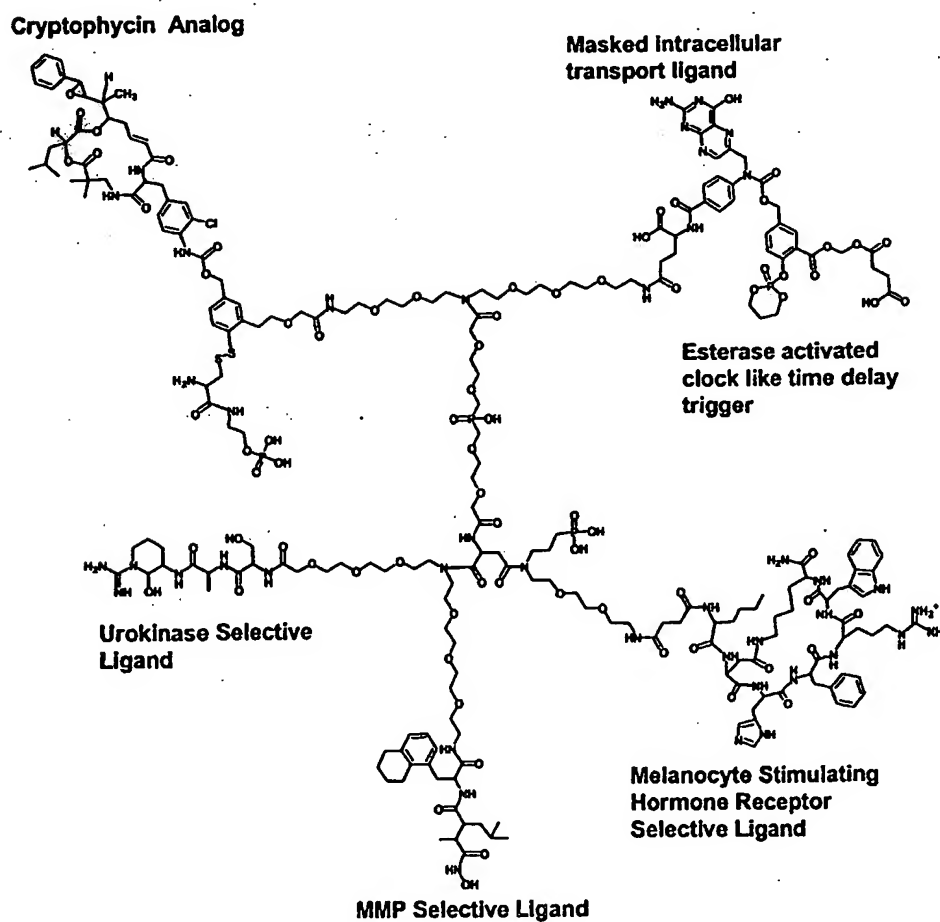
entirety.

Compound 23.2b may be prepared by treating compound 14.11.3 with phosgene in an inert solvent.

20

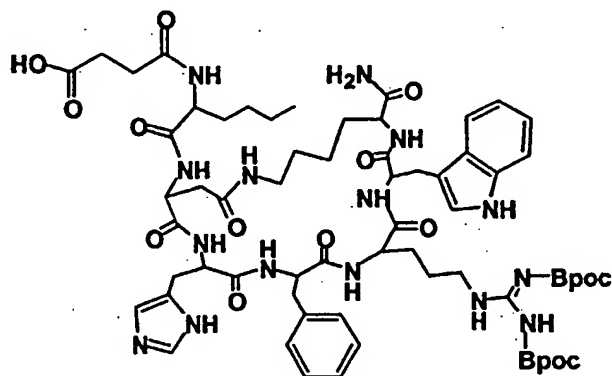
Example 24

Compound 24 is a multifunctional drug delivery vehicle with targeting ligands for urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1) and melanocyte stimulating hormone receptor. The drug has a masked folic acid group as an intracellular transport ligand, which will be activated by esterase. A derivative of cryptophycin, which is toxic at picomolar concentrations, will be freed upon cleavage of a disulfide trigger by thiol reductases. The drug is expected to have activity against malignant melanoma.

**Compound 24**

Compound 24 may be prepared by replacing compound 23.1 with compound 24.1 in the method described for the synthesis of compound 23. Also in this example, final deprotection should include an additional treatment with dilute acid to remove the 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc).

5



Compound 24.1

Compound 24.1 may be prepared using routine methods of peptide synthesis.

The phenylalanine residue has the D configuration. The other amino acids have

10 the L-configuration. The following references relate to this subject matter:

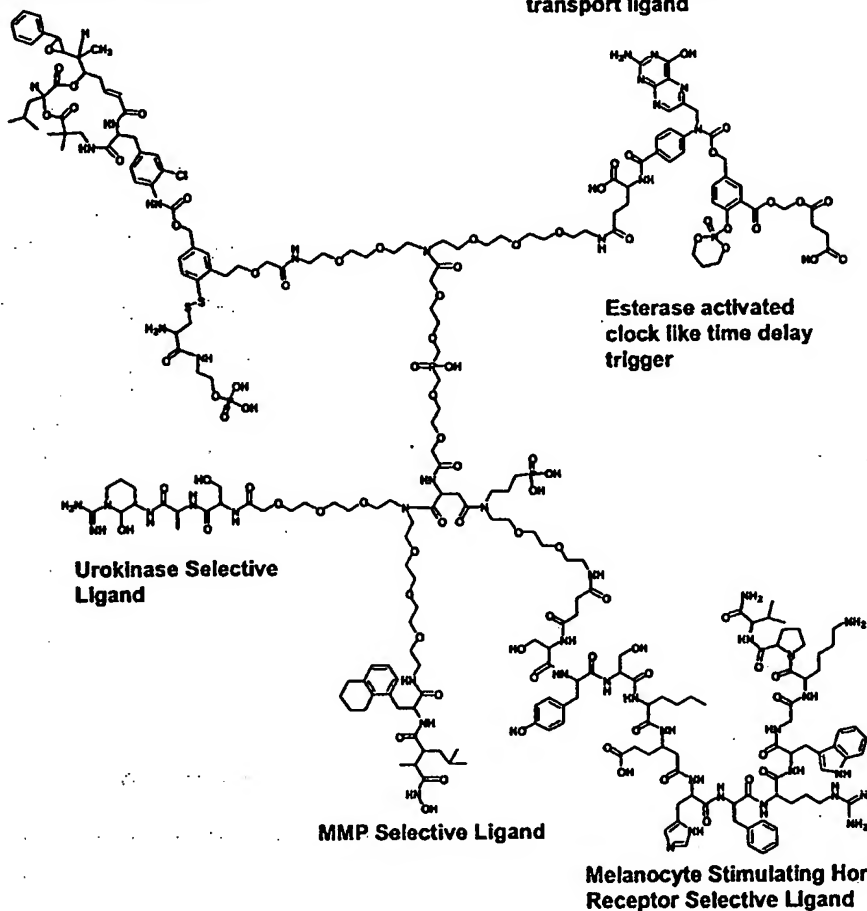
Haskell-Luevano C., et al., "Biological and Conformational Examination of Stereochemical Modifications Using the Template Melanotropin Peptide, Ac-Nle-c[Asp-His-Phe-Arg-Trp-Ala-Lys]-NH₂, on Human Melanocortin Receptors," *J Med Chem*, 40:1738-1748 (1997); Bednarek M.A., et al., "Structure-function Studies
15 on the Cyclic Peptide MT-II, Lactam Derivative of α -melanotropin," *Peptides*, 20:401-409 (1999), the contents of which are incorporated herein by reference in their entirety.

Example 25

Compound 25 is similar to compound 24 except that a different melanocyte stimulating hormone receptor selective ligand is employed.

Cryptophycin Analog

Masked intracellular transport ligand



Compound 25

5

Compound 25 may be prepared as described for compound 24 replacing compound 24.1 with compound 25.1 which may be synthesized using routine techniques of peptide chemistry. The phenylalanine residue has the D configuration. The other amino acids have the L-configuration. The following

10 references relate to this subject matter: Haskell-Luevano C., et al.,

Peptides from the Melanocortin Receptor, hMC1R," *J Med Chem*, 39:432-435

(1996); Haskell-Luevano C., et al., "Biological and Conformational Examination

of Stereochemical Modifications Using the Template Melanotropin Peptide, Ac-

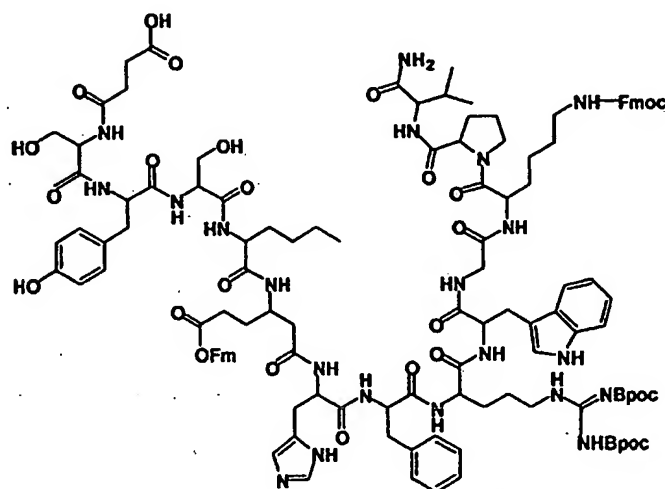
5 Nle-c[Asp-His-Phe-Arg-Trp-Ala-Lys]-NH₂, on Human Melanocortin Receptors," *J*

Med Chem, 40:1738-1748 (1997); Bednarek M.A., et al., "Structure-function

Studies on the Cyclic Peptide MT-II, Lactam Derivative of α -melanotropin,"

Peptides, 20:401-409 (1999), the contents of which are incorporated herein by reference in their entirety.

10



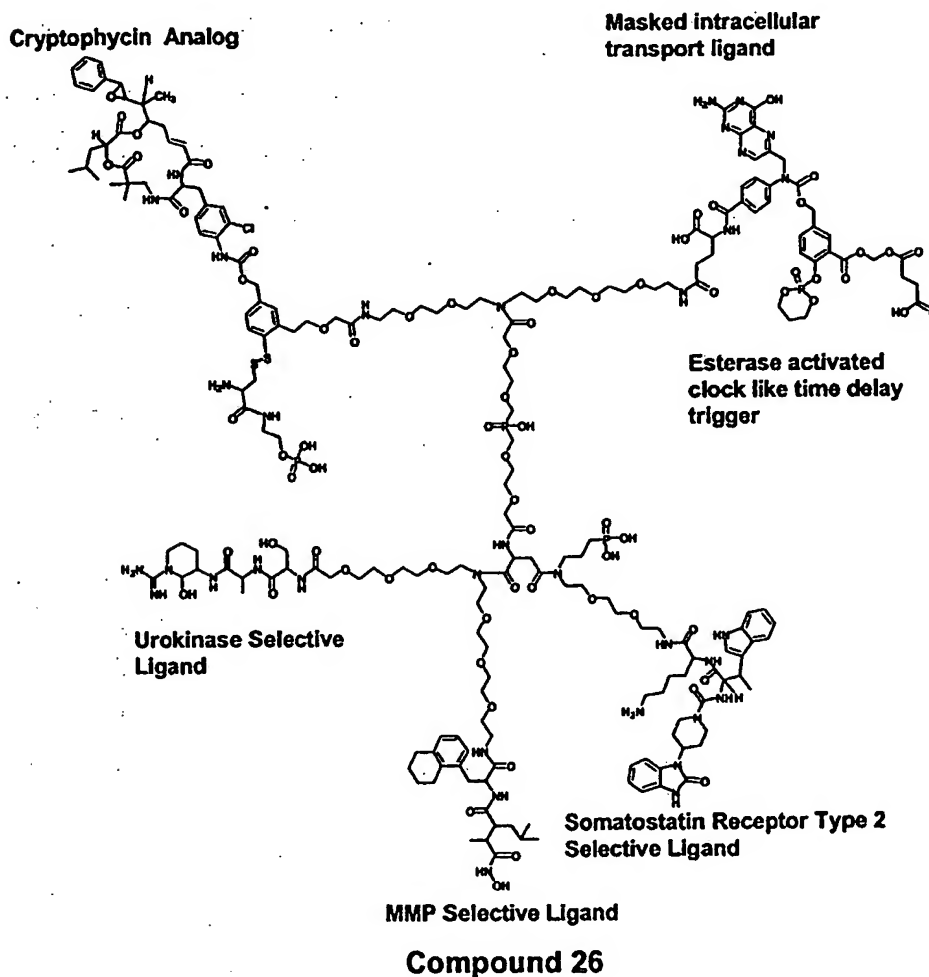
Compound 25.1

Example 26

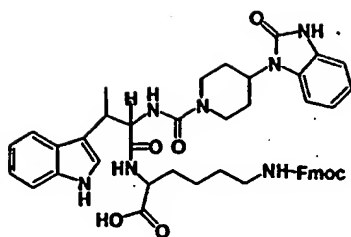
15 Compound 26 is similar to compound 23 but has targeting ligands for urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1) and somatostatin receptor subtype2. The following references relate to this subject matter: Yang L., et al.,

"Synthesis and Biological Activities of Potent Peptidomimetics Selective for Somatostatin Receptor Subtype 2," *Proc Natl Acad Sci USA*, 95(18):10836-41 (1998), the contents of which are incorporated herein by reference in their entirety.

5



Compound 26 may be prepared by substituting compound 26.1 for compound 24.1 in the method described for the preparation of compound 24.

**Compound 26.1**

Compound 26.1 may be prepared by treating the corresponding t-butyl ester with 9H-fluoren-9-ylmethyl chloroformate in the presence of a base such as pyridine in an inert solvent followed by treatment with trifluoroacetic acid to cleave the t-butyl ester. The t-butyl ester derivative is a known compound. The following references relate to this subject matter: Yang L., et al., "Synthesis and Biological Activities of Potent Peptidomimetics Selective for Somatostatin Receptor Subtype 2," *Proc Natl Acad Sci USA*, 95(18):10836-41 (1998), the contents of which are incorporated herein by reference in their entirety.

10

Example 27

Compound 27 is similar to compound 26, however a different somatostatin receptor selective ligand (Octreotide) is employed which binds with high affinity to SSTR2b, 3, 4, and 5. The following references relate to this subject matter: 4,395,403 7/26/83 Bauer, et al., "Polypeptides, Processes for their Production, Pharmaceutical Compositions Comprising Said Polypeptides and their Use", the contents of which are incorporated herein by reference in their entirety.

20

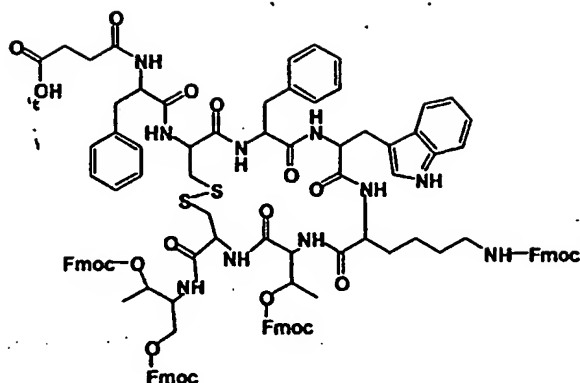
Cryptophycin Analog

Masked intracellular
transport ligandEsterase activated
clock like time delay
triggerUrokinase Selective
LigandSomatostatin Receptor
Selective Ligand

MMP Selective Ligand

Compound 27

Compound 27 may be prepared by the procedures described for compound 24 by substituting compound 27.1 for compound 24.1 in the synthetic scheme.



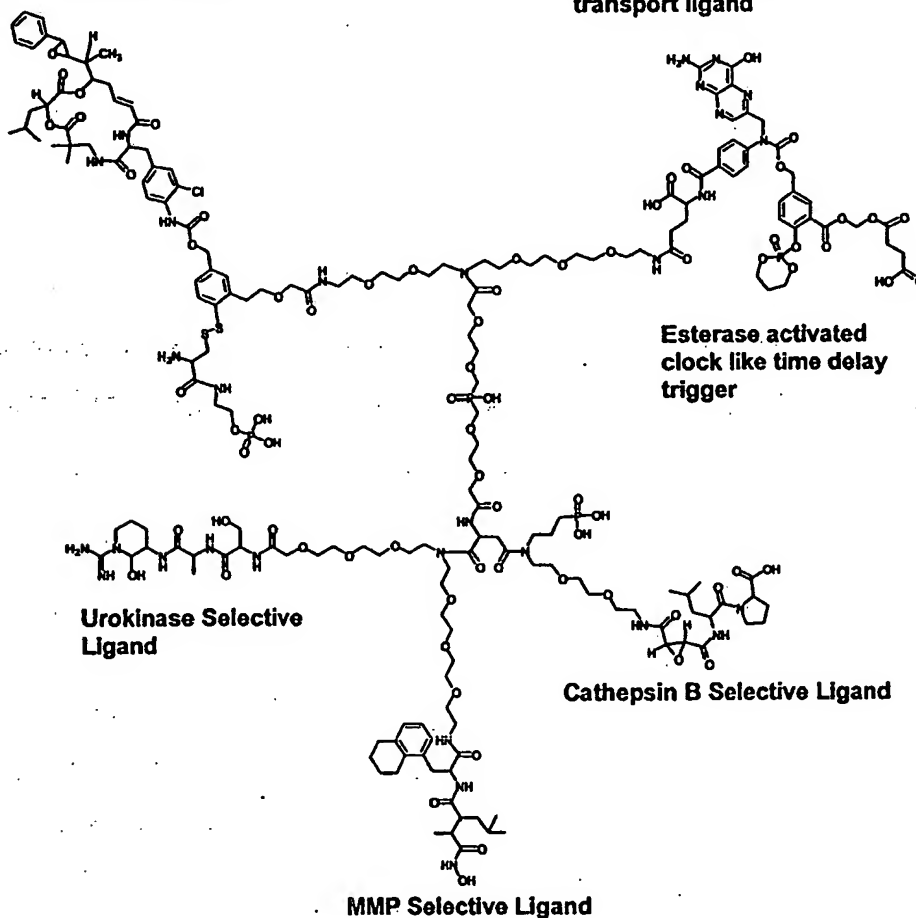
Compound 27.1

Example 28

- Compound 28 has targeting ligands for Cathepsin B, urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1). The drug has a masked folic acid as an intracellular transport ligand, and will release a cryptophycin analog upon activation of an intracellular trigger by thioreductase. The cathepsin B ligand will irreversibly bind to the enzyme and in the process will create neoantigens. The patient may be sensitized to these neoantigens to evoke a targeted immune response. Accordingly, this drug will provide dual mechanisms of tumor destruction: direct killing by the potent cryptophycin analog and indirect killing by an intense immune response against the neoantigens. The following references relate to this subject matter: Matsumoto K., et al., "X-Ray Crystal Structure of Papain Complexed with Cathepsin B-specific Covalent-type Inhibitor: Substrate Specificity and Inhibitory Activity," *Biochim Biophys Acta*, 1383:93-100 (1998); Towatari T., et al., "Novel Epoxysuccinyl Peptides. A Selective Inhibitor of Cathepsin B, in Vivo," *FEBS*, 280(2):311-315 (1991); Yamamoto A., et al., "Binding Mode of CA074, a Specific Irreversible Inhibitor, to Bovine Cathepsin B as Determined by X-Ray Crystal Analysis of the Complex," *J*

Biochem, 121:974-977 (1997); Gour-Salin B.J., et al., "Epoxysuccinyl Dipeptides as Selective Inhibitors of Cathepsin B," *J Med Chem*, 36:720-725 (1993), the contents of which are incorporated herein by reference in their entirety.

Cryptophycin Analog

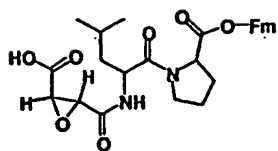
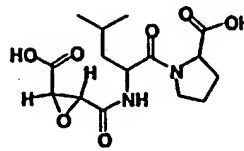
Masked Intracellular
transport ligand

MMP Selective Ligand

Compound 28

5

Compound 28 may be prepared by methods described for compound 24 by substituting compound 28.1 for compound 24.1 in the synthesis.

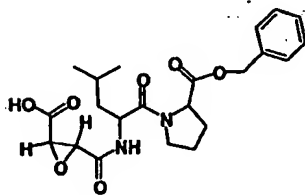
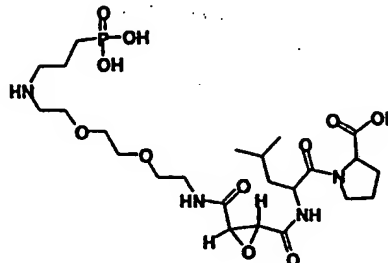
**Compound 28.1****Compound 28.1.1**

Compound 28.1 may be prepared from the known compound 28.2. The

following references relate to this subject matter: Gour-Salin B.J., et al.,

"Epoxysuccinyl Dipeptides as Selective Inhibitors of Cathepsin B," *J Med Chem*,

- 5 36:720-725 (1993), the contents of which are incorporated herein by reference in their entirety.

**Compound 28.2****Compound 28.3**

- 10 Esterification of compound 28.2 with (1,1-Dioxo-1H-1λ6-benzo[b]thiophen-2-yl)-methanol and dicyclohexylcarbodiimide, followed by catalytic hydrogenation with palladium on carbon to remove the benzyl group, followed by esterification with (9H-Fluoren-9-yl)-methanol and dicyclohexylcarbodiimide, followed by selective
- 15 28.1.

The neoantigens (and neoantigen precursors) to be used to sensitize patients in the method of targeted immunotherapy with compound 28 may be prepared by

incubating human cathepsin B with a compound such as compound 28.3 or compound 28.1.1. Alternatively, synthetic oligopeptides containing approximately 7-20 amino acids corresponding to the amino acid sequence of cathepsin B that contain the cysteine alkylated by the epoxide may be prepared and alkylated with compound 28.3 or compound 28.1.

Example 29

Compound 29 is similar to compound 28, however the linker to the Cathepsin B selective ligand has a disulfide bond that may provide a more facile catabolic route and facilitate neoantigen formation.

Cryptophycin Analog

Masked Intracellular transport ligand

Esterase activated clock like time delay trigger

Urokinase Selective Ligand

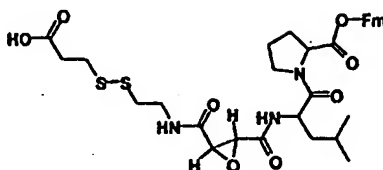
Cathepsin B Selective Ligand

MMP Selective Ligand

Compound 29

Compound 29 may be prepared by the methods for compound 28 by substituting compound 29.1 for compound 28.1.

5



Compound 29.1

Compound 29.1 may be prepared by reacting compound 28.1 with N-hydroxysuccinimide and dicyclohexylcarbodiimide in an inert solvent and then
10 reacting this active ester with 3-(2-Amino-ethyl(disulfanyl))-propionic acid and base in an inert solvent.

The neoantigens (and neoantigen precursors), to be employed for sensitization for use with the method of targeted neoantigen immunotherapy with compound
15 29, may be prepared in an analogous manner as described for compound 28.

Examples 30a, 30b and 30c

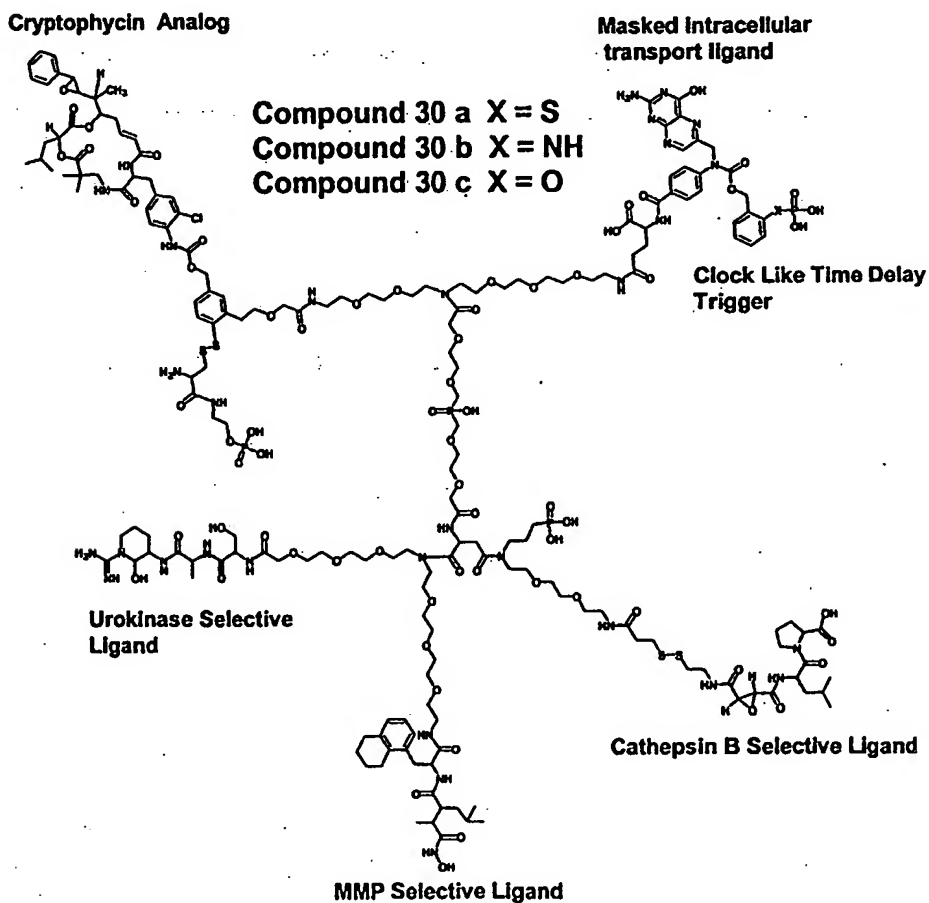
Compounds 30a 30b and 30c are similar to compound 29, however different
20 clock like time delayed triggers are employed to unmask the intracellular transport ligand. Ortho positioned electron donating groups promote elimination of benzylic compounds at rates that are slower than the corresponding para

derivatives and provide for a time delay clock like trigger. For example, under conditions in which para thio-benzyl carbamates undergo elimination with a half life of 10 minutes the corresponding ortho derivative has a half life of 72 min.

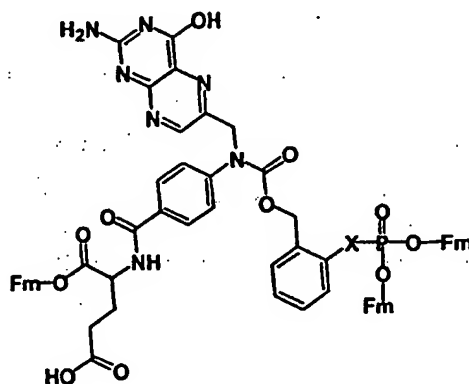
Similar behavior is expected for ortho hydroxy, and ortho amino benzylic

- 5 derivatives. The following references relate to this subject matter: Senter, Peter D., et al., "Development of a Drug-Release Strategy Based on the Reductive Fragmentation of Benzyl Carbamate Disulfides," *J Org Chem*, 55:2975-2978 (1990), the contents of which are incorporated herein by reference in their entirety.

10



Compounds 30a, 30b, and 30c may be prepared by substituting compound 30a.1, 30b.1 and 30c.1 respectively for compound 6.2.0b in the procedure described for compound 29.

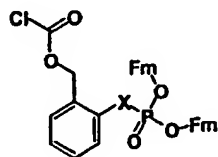


Compound 30a.1 $x = s$

Compound 30b.1 $x = NH$

Compound 30c.1 $x = o$

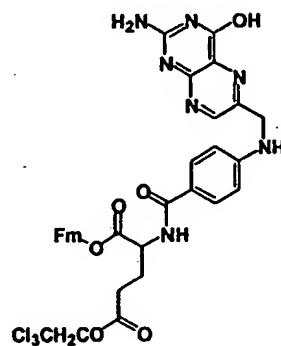
- 5 Compound 30a.1, 30b.1 and 30c.1 may be prepared by reacting compounds 30a.2, 30b.2 and 30c.2 respectively with compound 30.3 in an inert solvent in the presence of a base such as pyridine, and then cleaving the 2,2,2 trichloroethyl ester with Zn and phosphate buffer.



Compound 30a.2 $x = s$

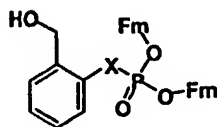
Compound 30b.2 $x = NH$

Compound 30c.2 $x = o$



Compound 30.3

Compounds 30a.2, 30b.2, and 30c.2 may be prepared by treating the corresponding benzylic alcohol compounds 30a.3, 30b.3 and 30c.3 with phosgene in an inert solvent.



Compound 30a.3 $x = s$

Compound 30b.3 $x = NH$

Compound 30c.3 $x = o$

- 5 Compound 30a.3 may be prepared by treating 2-trityloxymethyl-benzenethiol with phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester and base in an inert solvent followed by acid treatment.

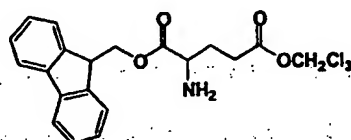
- 10 The compound 2-trityloxymethyl-benzenethiol may be prepared by reacting [2-(2-Hydroxymethyl-phenyldisulfanyl)-phenyl]-methanol with trityl chloride and base in an inert solvent and then reducing the disulfide bond with a reagent such as sodium borohydride.

- 15 Compound 30b.3 may be prepared by treating 2-aminobenzyl alcohol with chlorotrimethylsilane and base, and then reacting with phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester and base in an inert solvent, followed by hydrolysis of the silyl groups.

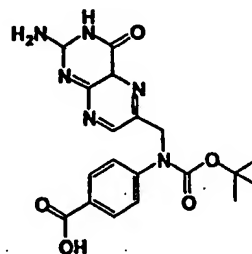
- 20 Compound 30c.3 may be prepared by treating 2-Hydroxy-benzaldehyde with phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester and base in an inert solvent, followed by reduction of the aldehyde to the alcohol. The reduction may

be carried out by selective hydrogenation with palladium on carbon or by a reagent such as sodium borohydride.

Compound 30.3 may be prepared by a multi-step procedure. Compound 20.8.3c
5 and compound 30.3a may be coupled. Treating the product with acid will remove the t-Boc group and give compound 30.3.



Compound 20.8.3c



Compound 30.3a

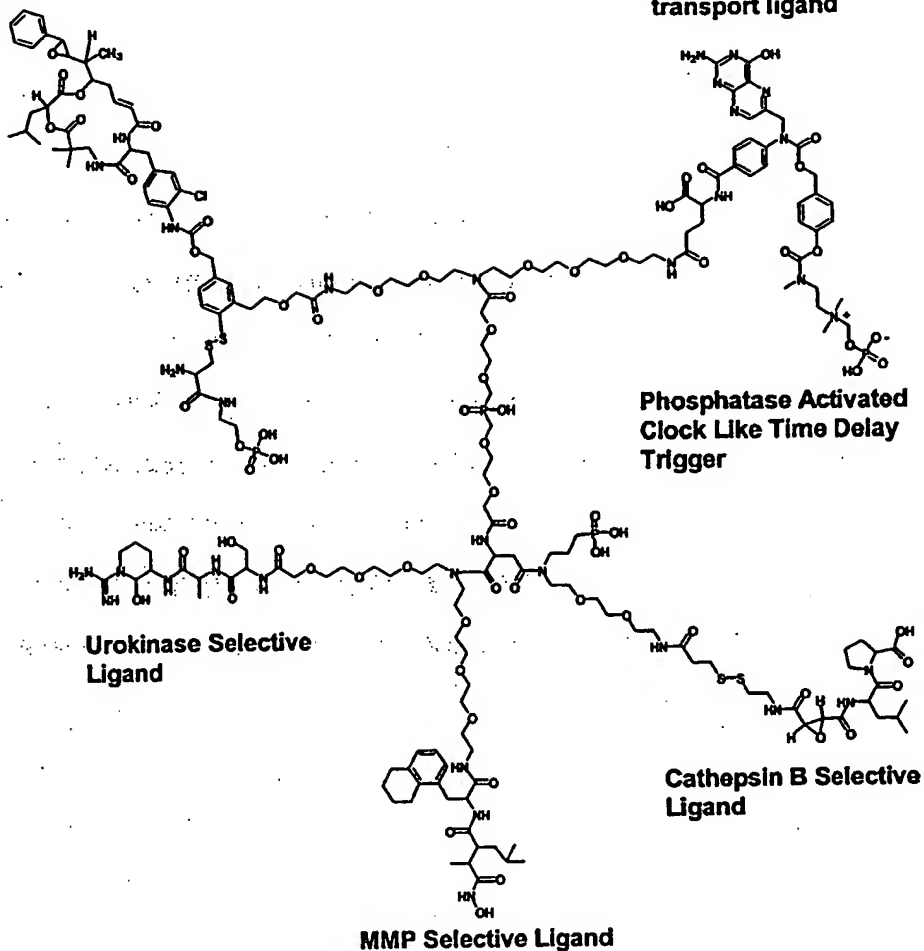
Compound 30.3a may be prepared by treating pteric acid with a reagent such
10 as di-t-butyl pyrocarbonate in an inert solvent.

In an alternate method for the preparation of compound 30.3, pteric acid may be treated with an excess of a reagent such as hexamethyldisilazane and a catalytic amount of chlorotrimethylsilane in an inert solvent. The silylated
15 derivative may then be reacted with (1,1-Dioxo-1H-1λ6-benzo[b]thiophen-2-yl)-methyl chloroformate in an inert solvent. After hydrolysis of the silyl groups, the product may be coupled to compound 20.8.3c. Selective removal of the Bsmoc group with tris(2-aminoethyl)-amine will give compound 30.3.

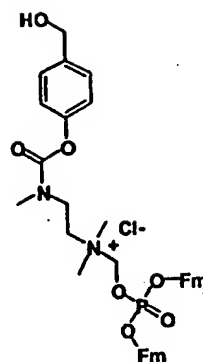
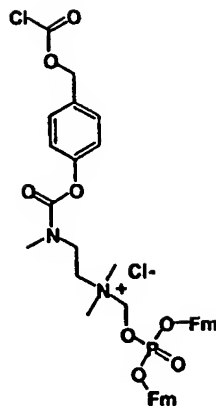
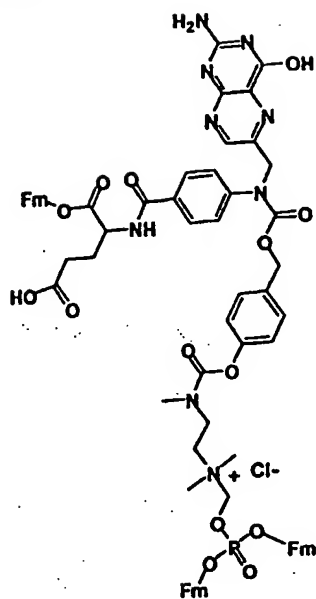
20

Example 31

Compound 31 is similar to compound 30 but a different cyclization based phosphatase activated time delayed clock like trigger is employed to unmask the intracellular transport ligand. Phosphatase will cleave the phosphoester and formaldehyde will be eliminated, thereby converting the nonnucleophilic quaternary ammonium group into a nucleophilic tertiary amino group. The tertiary amino group will then catalyze the hydrolysis of the carbamate by a cyclic intermediate with a half life of approximately 40 minutes. The following references relate to this subject matter: Saari W.S., et al., "Cyclization-Activated Prodrugs. Basic Carbamates of 4-Hydroxyanisole," *J Med Chem*, 33:97-101 (1990); Krise J. P., et al., "Novel Prodrug Approach for Tertiary Amines: Synthesis and Preliminary Evaluation of N-Phosphonooxymethyl Prodrugs," *J Med Chem*, 42:3094-3100 (1999); Krise J.P., et al., "A Novel Prodrug Approach for Tertiary Amines. 3. In Vivo Evaluation of Two N-Phosphonooxymethyl Prodrugs in Rats and Dogs," *J Pharm Sciences*, 88(9):928-932 (1999), the contents of which are incorporated herein by reference in their entirety.

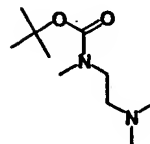
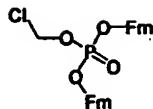
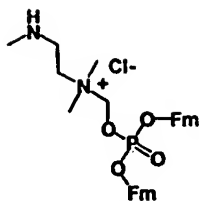
Cryptophycin Analog**Masked intracellular
transport ligand****Compound 31**

Compound 31 may be prepared by substituting compound 31.1 for compound 30c.1 in the process described for the synthesis of compound 30c.



Compound 31.1 Compound 31.2 Compound 31.3

- Compound 31.1 may be prepared by reacting compound 31.2 and compound
- 5 30.3 and then cleaving the 2,2,2 trichloroethyl ester with Zn. Compound 31.2 may be prepared by reacting compound 31.3 with phosgene in an inert solvent.
- Compound 31.3 may be prepared by reduction of the corresponding aldehyde (compound 31.4) with hydrogen and palladium on carbon or with a reagent such as sodium borohydride. Compound 31.4 may be prepared by reacting p-
- 10 hydroxybenzaldehyde with phosgene in an inert solvent and then reacting the resulting chloroformate with compound 31.5 in an inert solvent in the presence of a base such as pyridine.



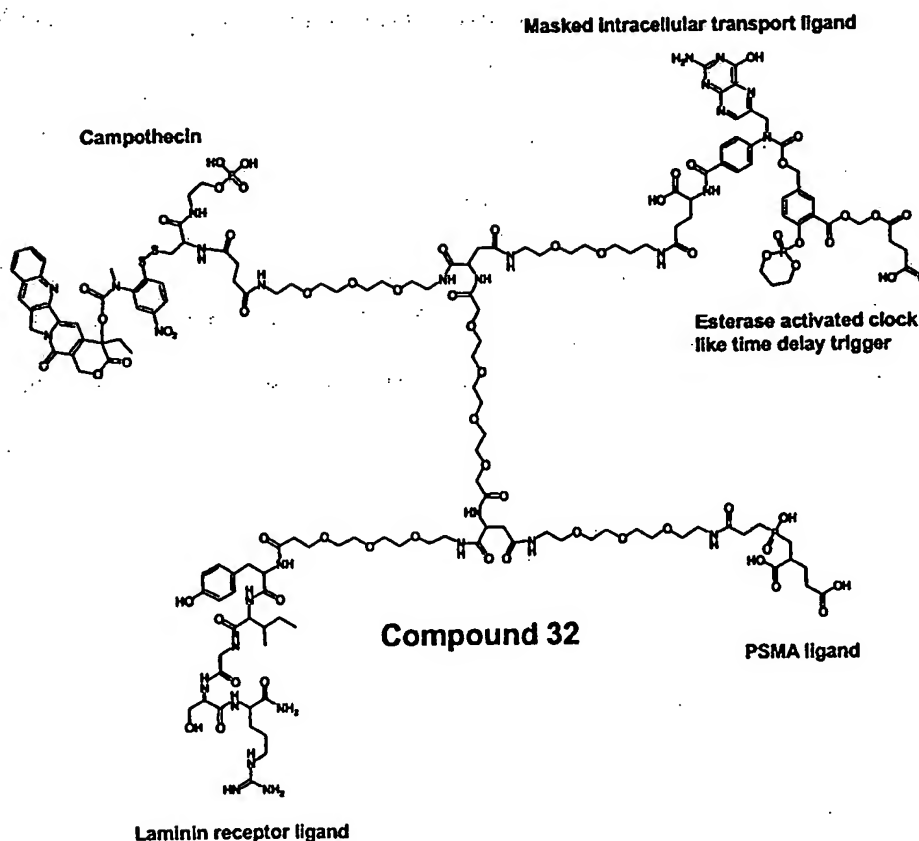
Compound 31.5 Compound 31.6 Compound 31.7

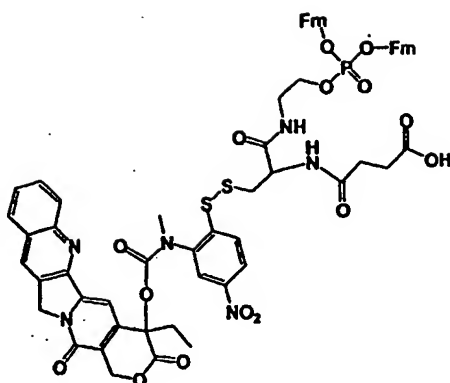
Compound 31.5 may be prepared by reacting compounds 31.6 and 31.7 in an inert solvent and then treating with acid to remove the t-Boc group. Compound 31.6 may be prepared by alkylating tetramethyl-ammonium bis-(9H-fluoren-9-ylmethyl) phosphate with chloriodomethane in an inert solvent. Compound 31.7 may be prepared by treating N,N,N'-trimethyl-ethane-1,2-diamine with di-t-butylpyrocarbonate and in an inert solvent. The following references relate to this subject matter: Saari W.S., et al., "Cyclization-Activated Prodrugs. Basic Carbamates of 4-Hydroxyanisole," *J Med Chem*, 33:97-101 (1990); Krise J. P., et al., "Novel Prodrug Approach for Tertiary Amines: Synthesis and Preliminary Evaluation of N-Phosphonooxymethyl Prodrugs," *J Med Chem*, 42:3094-3100 (1999); Krise J.P., et al., "A Novel Prodrug Approach for Tertiary Amines. 3. In Vivo Evaluation of Two N-Phosphonooxymethyl Prodrugs in Rats and Dogs," *J Pharm Sciences*, 88(9):928-932 (1999), the contents of which are incorporated herein by reference in their entirety.

Example 32

Compound 32 has targeting ligands for PSMA and laminin receptor. It has a clock like esterase activated time delayed trigger that will function to unmask the intracellular transport ligand. Esterase will unmask a carboxylate group situated ortho to the phosphotriester group. The carboxylate group will, by an

intramolecular nucleophilic reaction, cleave the phosphotriester, thereby unmasking the phenolic hydroxy group. The intramolecular nucleophilic reaction is expected to proceed with a half life of approximately 90 minutes under physiological conditions. The cytotoxic agent, camptothecin, will be released upon activation of an intracellular trigger. The following references relate to this subject matter: Bromilow R.H., et al., "Intramolecular Catalysis of Phosphate Triester Hydrolysis. Nucleophilic Catalysis by the Neighbouring Carboxyl Group of the Hydrolysis of Dialkyl 2-Carboxyphenyl Phosphates," *J Chem Soc*, 1091-1096 (1971), the contents of which are incorporated herein by reference in their entirety.



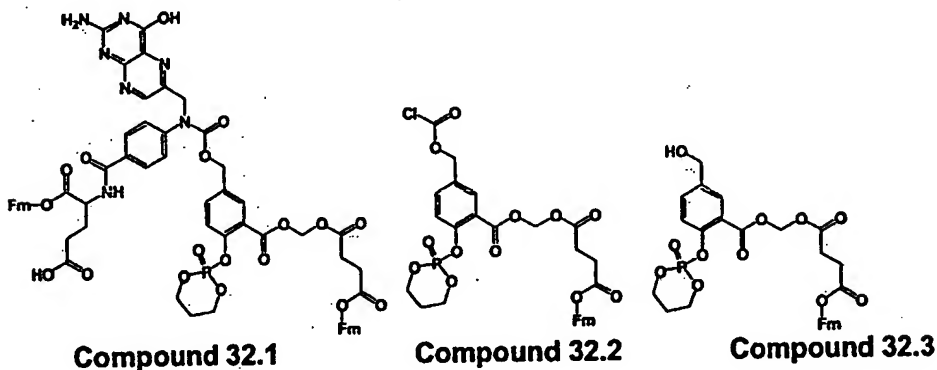
**Compound 32.9**

Compound 32 may be prepared by the methods described for compound 6 by replacing compound 6.2.0c with compound 32.9.

5

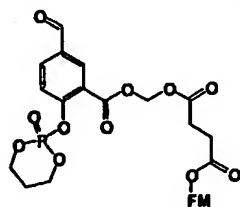
Synthesis of compound 32.1

Compound 32.1 may be prepared by a multi-step process.

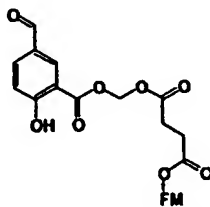


- 10 Compound 32.1 may be prepared by reacting compound 32.2 and compound 30.3 in an inert solvent in the presence of a base such as pyridine and then cleaving the 2,2,2 trichloro-ethyl ester with Zn. Compound 32.2 may be prepared by treating compound 32.3 with phosgene in an inert solvent. Compound 32.3

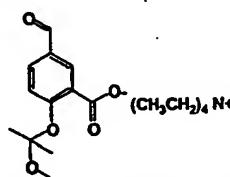
may be prepared by reduction of the aldehyde compound 32.4 with hydrogen and palladium catalyst or a reagent such as sodium borohydride.



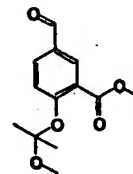
Compound 32.4



Compound 32.5



Compound 32.6



Compound 32.7

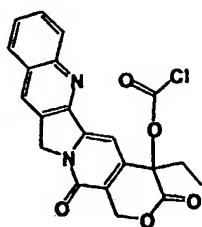
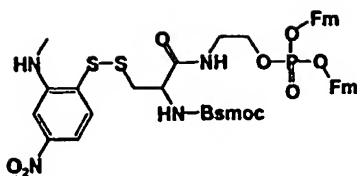
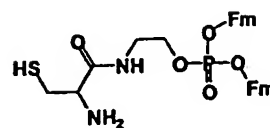
- 5 Compound 32.4 may be prepared by reacting compound 32.5 and 2-chloro-[1,3,2]dioxaphosphinane 2-oxide in an inert solvent in the presence of base.

Compound 32.5 may be prepared by reacting compound 32.6 and succinic acid chloromethyl ester 9H-fluoren-9-ylmethyl ester in an inert solvent and then treating with dilute acid to selectively cleave the 1-methyl-1-methoxyethyl ether.

- 10 (Alternatively, the silver salt of compound 32.6 may be employed). Succinic acid chloromethyl ester 9H-fluoren-9-ylmethyl ester may be prepared by treating succinic acid mono-(9H-fluoren-9-ylmethyl) ester with chloriodomethane in an inert solvent.

15 Synthesis of compound 32.9

Compound 32.9 may be prepared by reacting compound 32.10 and compound 32.11 in an inert solvent in the presence of a base such as pyridine and then selectively removing the Bsmoc group with tris(2-aminoethyl)-amine, and then reacting with succinic anhydride in an inert solvent.

**Compound 32.10****Compound 32.11****Compound 32.12**

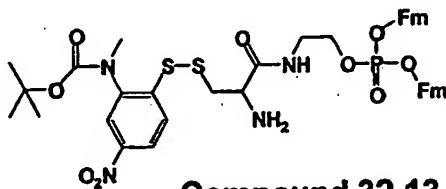
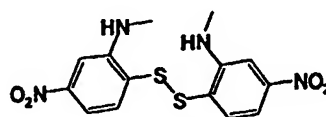
Compound 32.10 may be prepared by treating camptothecin with phosgene in an inert solvent.

5

Compound 32.11 may be prepared by a multi-step process. Reacting (2-Mercapto-5-nitro-phenyl)-methyl-carbamic acid tert-butyl ester with diethyl azidocarboxylate in an inert solvent and then reacting the product with compound 32.12 will give compound 32.13. Treatment with (1,1-Dioxo-1H-1λ6-

10

benzo[b]thiophen-2-yl)-methyl chloroformate and base in an inert solvent, followed by treatment with acid to cleave the t-Boc group, will give compound 32.11.

**Compound 32.13****Compound 32.14**

15 The compound (2-Mercapto-5-nitro-phenyl)-methyl-carbamic acid tert-butyl ester may be prepared by treating compound 32.14 with di-t-butyl pyrocarbonate in an inert solvent and then reducing the disulfide bond with a reagent such as sodium borohydride.

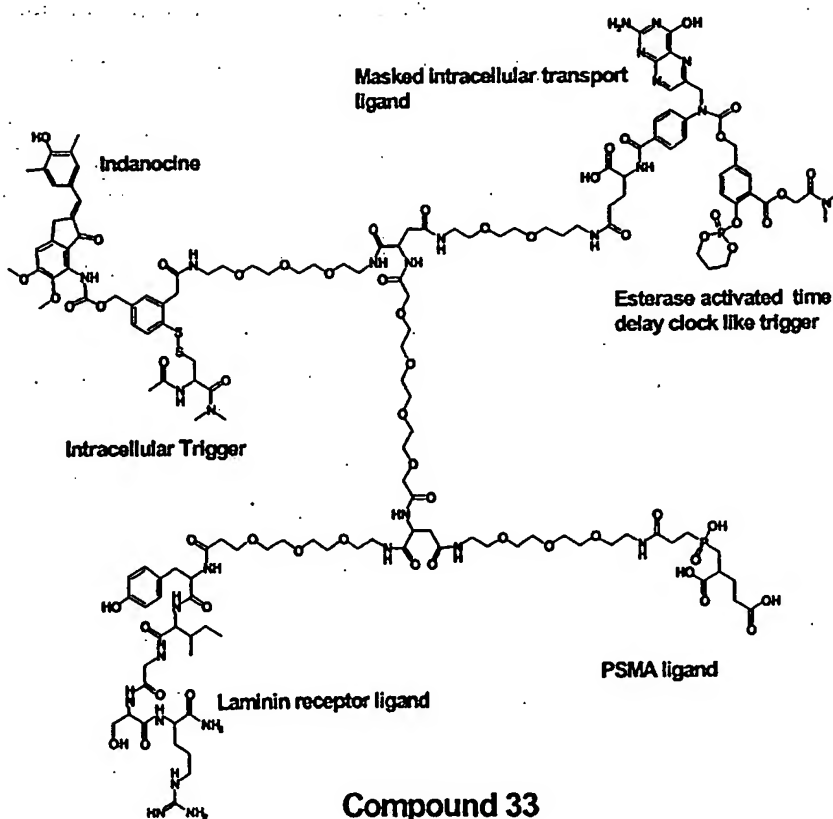
Example 33

Compound 33 is similar to compound 6, however compound 33 has a different type of esterase activated time delay clock like trigger, which will unmask the intracellular transport ligand. The esters of N,N-disubstituted hydroxyacetamides

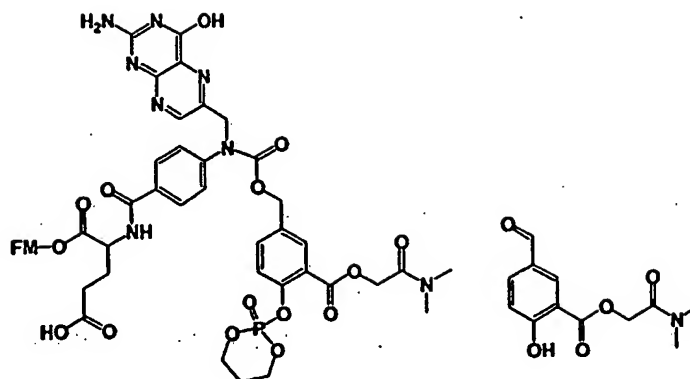
- 5 are very rapidly cleaved by esterase. The triggering mechanisms are similar to those described for compound 32. The following references relate to this subject matter: Bundgaard H.; Nielsen N.M., "Esters of N,N-Disubstituted 2-

Hydroxyacetamides as a Novel Highly Biolabile Prodrug Type for Carboxylic Acid Agents," *J Med Chem*, 30(3):450-453 (1987), the contents of which are

10 incorporated herein by reference in their entirety.



Compound 33

**Compound 33.1****Compound 33.2**

Compound 33 may be prepared by replacing compound 6.2.0b with compound 33.1 in the procedure described for the synthesis of compound 6. Compound 33.1 may be made by the procedure described for compound 32.1 by

- 5 substituting compound 33.2 for compound 32.5. Compound 33.2 may be prepared by coupling compound 32.6 and 2-hydroxy-N,N-dimethyl-acetamide and then treating with acid to cleave the 1-methyl-1-methoxyethyl ether.

10 Example 34

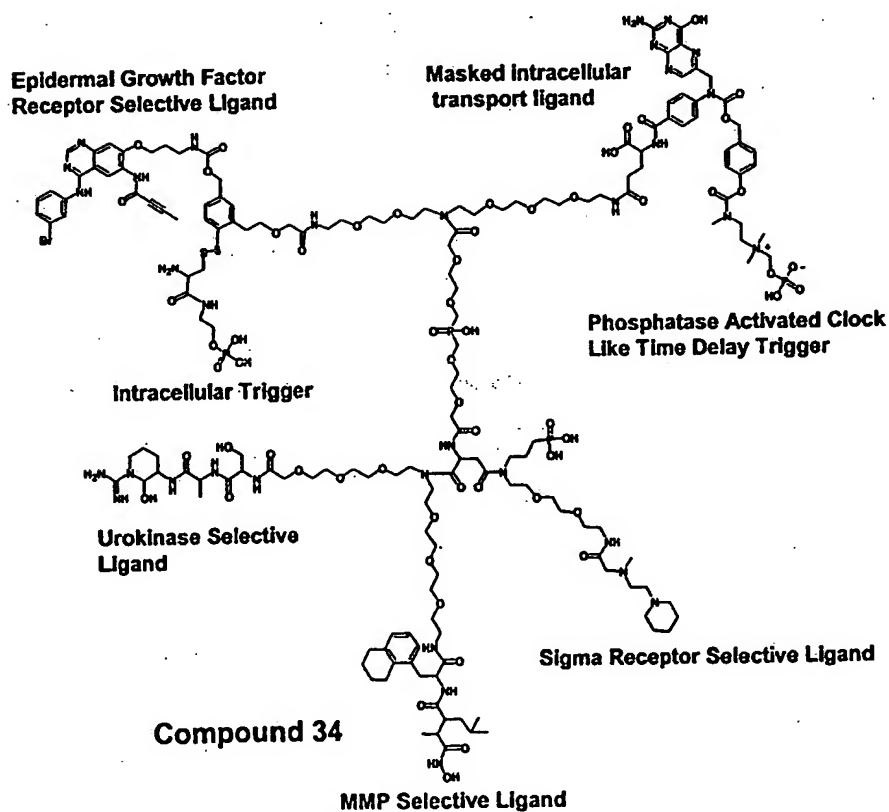
Compound 34 is a multifunctional drug delivery vehicle for use in the method of targeted neoantigen immunotherapy against epidermal growth factor receptors. It has targeting ligands for sigma receptors, urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1) and epidermal growth factor receptors including

- 15 erB2. The drug has a masked folic acid as an intracellular transport ligand with a phosphatase activated time delay clock like trigger. Thioreductase will activate an intracellular trigger and release a compound that will irreversibly bind to the epidermal growth factor receptors and generate neoantigen precursors. The patient may be sensitized to these epidermal growth factor based neoantigens to

evoke a targeted immune response against the tumor. The following references relate to this subject matter: Discafani C.M., et al., "Irreversible Inhibition of Epidermal Growth Factor Receptor Tyrosine Kinase with *In Vivo* Activity by N-[4-[(3-Bromophenyl)amino]-6-quinazolinyl]-2-butyramide (CL-387,785)," *Biochem*

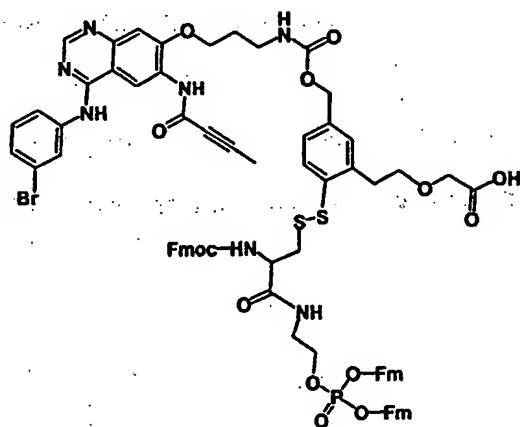
5 *Pharm*, 57:917-925 (1999); Smaill J.B., et al., "Tyrosine Kinase Inhibitors. 17. Irreversible Inhibitors of the Epidermal Growth Factor Receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides Bearing Additional Solubilizing Functions," *J Med Chem*, 43:1380-1397 (2000), the contents of which are incorporated herein by reference in their

10 entirety.

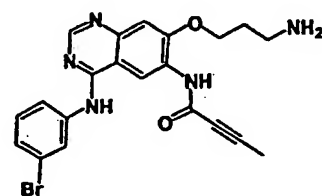


Compound 34 may be prepared by the methods described for the synthesis of compound 21 by replacing compound 21.2.2e with compound 14.5, then replacing compound 21.1.2 with compound 34.1 and also replacing compound 6.2.0b with compound 31.1.

5



Compound 34.1

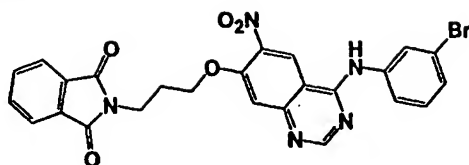
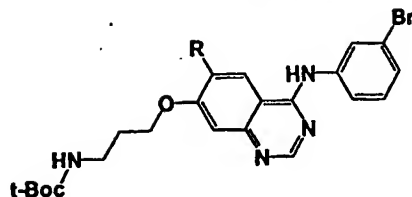


Compound 34.2

Compound 34.1 may be prepared by reacting compound 34.2 and compound 23.2b in an inert solvent in the presence of a base such as pyridine and then treating with tris(2-aminoethyl)-amine to cleave the Bsm ester.

10

Compound 34.2 may be prepared by a multi-step process. Reacting (3-bromophenyl)-(7-fluoro-6-nitro-quinazolin-4-yl)-amine and 2-(3-Hydroxy-propyl)-isoindole-1,3-dione in the presence of a strong base such as sodium hydride in an inert solvent will give compound 34.3.

**Compound 34.3**
Compound 34.4a R = nitro
Compound 34.4b R = amino

Removal of the phthalyl protecting group, followed by treatment with di-*t*-butyl pyrocarbonate and in an inert solvent will give compound 34.4a. Suitable reagents that are compatible with the nitro group to accomplish the deprotection are well known. The following references relate to this subject matter: Greene, Theodora W.; Wuts, Peter G.M. (1999) "Protective Groups in Organic Synthesis" John Wiley & Sons, Inc. p 565, the contents of which are incorporated herein by reference in their entirety.

- 5
- 10 Catalytic hydrogenation of the nitro group with palladium on carbon will give compound 34.4b. Treatment with the mixed anhydride formed between but-2-ynoic acid and isobutyl chloroformate in an inert solvent in the presence of base, followed by treatment with acid to remove the *t*-Boc group will give compound 34.2. The following references relate to this subject matter: Discafani C.M., et
- 15 al., "Irreversible Inhibition of Epidermal Growth Factor Receptor Tyrosine Kinase with *In Vivo* Activity by *N*-[4-[(3-Bromophenyl)amino]-6-quinazolinyl]-2-butynamide (CL-387,785)," *Biochem Pharm*, 57:917-925 (1999); Smaill J.B., et al., "Tyrosine Kinase Inhibitors. 17. Irreversible Inhibitors of the Epidermal Growth Factor Receptor: 4-(Phenylamino)quinazoline- and 4-
- 20 (Phenylamino)pyrido[3,2-*d*]pyrimidine-6-acrylamides Bearing Additional Solubilizing Functions," *J Med Chem*, 43:1380-1397 (2000); 5,760,04, 6/02/98,

Wissner et al., "4-Aminoquinazoline EGFR Inhibitors", the contents of which are incorporated herein by reference in their entirety.

Patients may be sensitized to the epidermal growth factor receptor or erb2

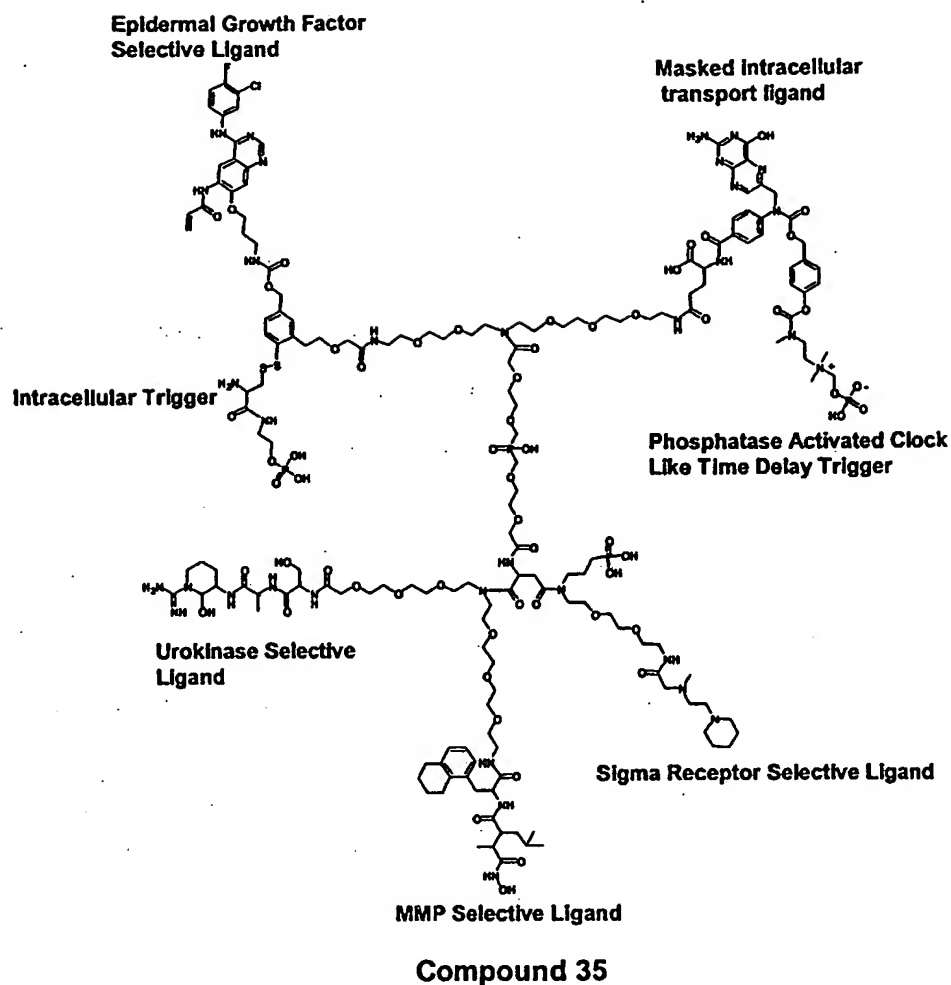
- 5 derived neoantigens by immunizing with epidermal growth factor receptors or erb2 that has been reacted with compound 34.2. Alternatively, synthetic oligopeptides that correspond to the amino acid sequence of the receptor with compound 34.2 covalently attached may be employed.

10

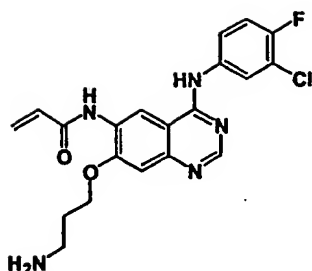
Example 35

Compound 35 is similar to compound 34, however a different group is employed to modify the epidermal growth factor receptor. The following references relate to this subject matter: Smaill J.B., et al., "Tyrosine Kinase Inhibitors. 17.

- 15 Irreversible Inhibitors of the Epidermal Growth Factor Receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides Bearing Additional Solubilizing Functions," *J Med Chem*, 43:1380-1397 (2000); Smaill J.B., et al., "Tyrosine Kinase Inhibitors. 15. 4-(Phenylamino)quinazoline and 4-(Phenylamino)pyrido[d]pyrimidine Acrylamides
- 20 as Irreversible Inhibitors of the ATP Binding Site of the Epidermal Growth Factor Receptor," *J Med Chem*, 42:1803-1815 (1999), the contents of which are incorporated herein by reference in their entirety.



Compound 35 may be prepared by the method described for compound 34 by
 5 replacing compound 34.2 with compound 35.1.

**Compound 35.1**

Compound 35.1 may be prepared by replacing (3-bromo-phenyl)-(7-fluoro-6-nitro-quinazolin-4-yl)-amine with (3-Chloro-4-fluoro-phenyl)-(7-fluoro-6-nitro-quinazolin-4-yl)-amine and by replacing but-2-ynoic acid with acrylic acid in the
5 procedure described for the synthesis of compound 34.

Patients may be sensitized to the neoantigens using compounds analogous to those described in example 34.

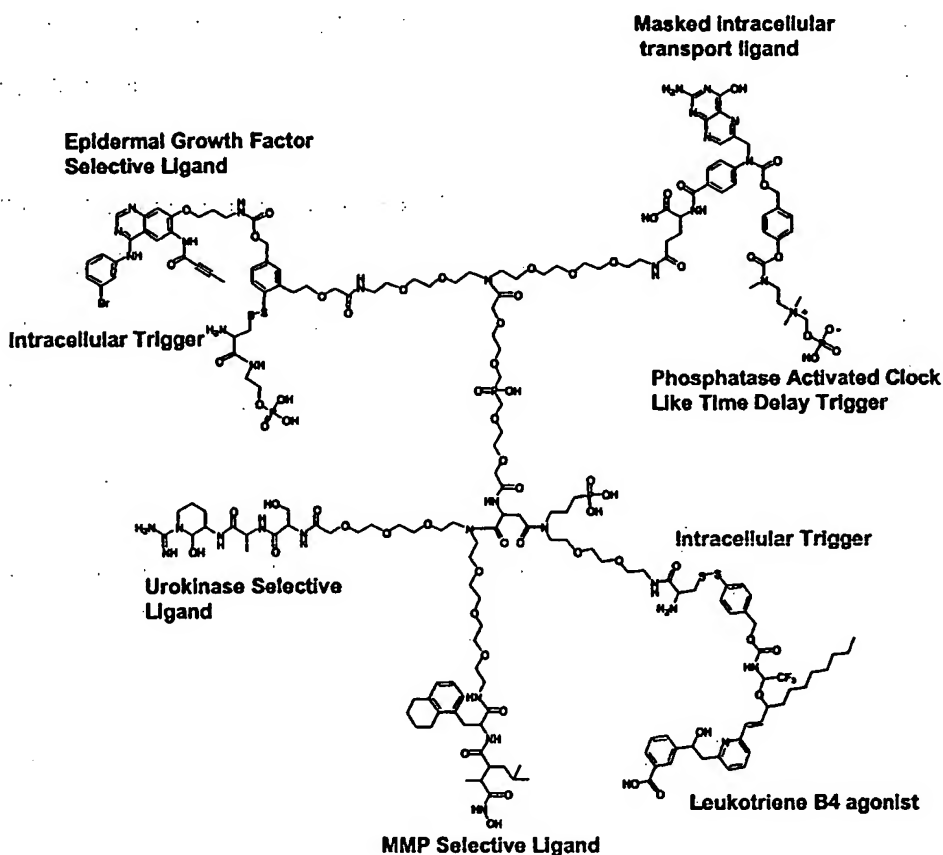
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Example 36

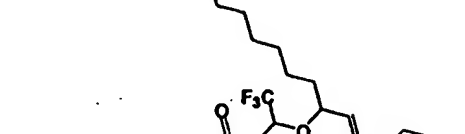
Compound 36 is a multifunctional drug delivery vehicle with ligands for urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1) and epidermal growth factor receptors including erbB2. The drug has a phosphatase activated
15 time delay clock like trigger that will unmask the intracellular transport ligand. The drug has an intracellular trigger that when cleaved by thioreductases will free a compound that will irreversible modify epidermal growth factor receptors and erb2 receptors and in the process generate neoantigens. In addition, the drug has another intracellular trigger, which when activated will release a
20 leukotriene receptor agonist. This leukotriene receptor agonist will, after diffusing out of the tumor cells, elicit a localized inflammatory response by

activating the innate immune system. This inflammatory reaction will synergize with the adaptive immune response generated against the neoantigens. The following references relate to this subject matter: Daines R.A., et al., "Trisubstituted Pyridine Leukotriene B4 Receptor Antagonists: Synthesis and Structure-Activity Relationships," *J Med Chem*, 36(22):3321-32 (1993);

5 Kingsbury W.D., et al., "Synthesis of Structural Analogs of Leukotriene B4 and their Receptor Binding Activity," *J Med Chem*, 36(22):3308-20 (1993), the contents of which are incorporated herein by reference in their entirety.




Compound 36

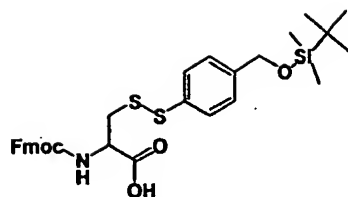
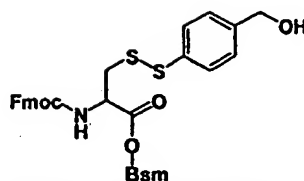


Chemical structure of Compound 36.1, a complex molecule featuring a long alkyl chain, a pyridine ring, a quaternary silicon atom, a carboxylic acid group, and a fluoromethyl (Fmoc) protecting group. The structure includes a long alkyl chain (CH₃(CH₂)₁₀CH₂-) attached to a pyridine ring via a vinyl ether linkage. The pyridine ring is also connected to a quaternary silicon atom (Si(CH₃)₃), which is further linked to a carboxylic acid group (COOH) and a fluoromethyl (Fmoc) protecting group. The molecule also contains a carboxylic acid group (COOH) and a fluoromethyl (Fmoc) protecting group.

5


Compound 36.2 is a complex molecule featuring a 1,3-dioxolane ring substituted with a Bsm group and a Fmoc group. It is linked via a thioether bridge to a benzyl group, which is further connected to a carbamate group. The carbamate is substituted with a chlorine atom and a trifluoromethyl group. Compound 36.3 is a complex molecule featuring a pyridine ring substituted with a silyl ether group and a benzyl group. The benzyl group is linked via an ester bridge to a Fmoc group. The pyridine ring is further substituted with a long alkyl chain and a hydroxyl group.

Compound 36.2 may be prepared by a multi-step process. Reacting 4-(tert-Butyl-dimethyl-silanyloxymethyl)-benzenethiol with diethylazodicarboxylate in an inert solvent and then reacting the adduct with Fmoc -L- cysteine will form the mixed disulfide compound 36.4.

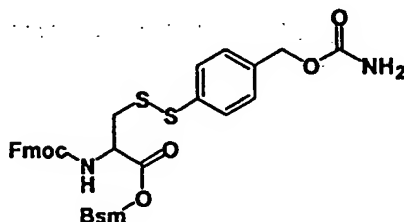
**Compound 36.4****Compound 36.5**

Treating with dicyclohexylcarbodiimide and (1,1-Dioxo-1H-1 λ 6-benzo[b]thiophen-2-yl)-methanol in an inert solvent will give the Bsm ester.

Treatment with acid will cleave the t-butyldimethyl silyl group and give compound

- 5 36.5. Treatment with phosgene in an inert solvent will give the chloroformate.

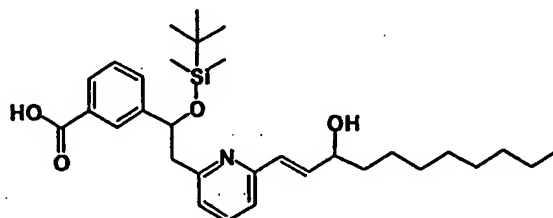
Treatment with ammonia, at low temperature in an inert solvent, will give compound 36.6.

**Compound 36.6**

- 10 Treatment of compound 36.6 with trifluoro-acetaldehyde in an inert solvent, followed by treatment with a reagent such as phosphorous trichloride will give compound 36.2. The following references relate to this subject matter:
- Weygand F., et al., "2,2,2-Trifluoro-1-acylaminoethyl Groups as Protective Groups for Imino Groups of Histidine in Peptide Synthesis," *Chem Ber*, 100(12):3841-9 (1967); Weygand, Friedrich; Steglich, Wolfgang; Pietta, Pier G., 15 *Chem Ber*, 99: p.1944 (1966), the contents of which are incorporated herein by reference in their entirety.

Compound 36.3 may be prepared by treating compound 36.7 with trityl chloride and base in an inert solvent and then reacting with (9H-Fluoren-9-yl)-methanol and dicyclohexylcarbodiimide in an inert solvent, followed by acid treatment to remove the trityl group.

5

**Compound 36.7**

The following references relate to this subject matter: Kingsbury W.D., et al., "Synthesis of Structural Analogs of Leukotriene B₄ and their Receptor Binding Activity," *J Med Chem*, 36(22):3308-20 (1993), the contents of which are

10 incorporated herein by reference in their entirety.

Example 37

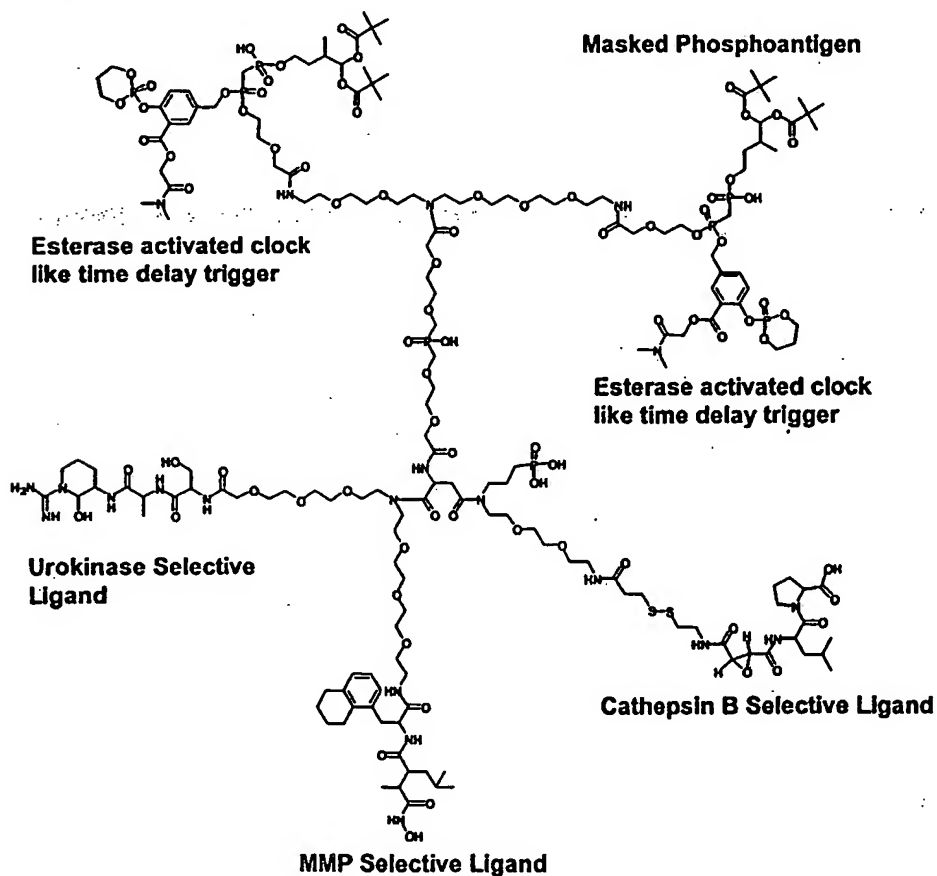
15 Compound 37 is a multifunctional drug delivery vehicle with targeting ligands for urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1) and cathepsin B. Like compound 29, this compound may be used for the method of targeted neoantigen generation where the neoantigens are derived from cathepsin B. Compound 37 also has two masked formyl butyl pyrophosphate analogs. 3-

20 formyl -1-butyl-pyrophosphate and related derivatives are extremely potent activators of γ/δ T cells. The formyl groups will be unmasked by the action of esterase. The pyrophosphate analog will be unmasked by an esterase

activated clock like trigger that will have a half life of about 90 minutes. Synergy between the innate and adaptive immune response is expected to augment the antitumor immune response. The following references relate to this subject matter: Belmont C, et al., "3-Formyl-1-butyl Pyrophosphate a Novel

5 Mycobacterial Metabolite-Activating Human Gammadelta T Cells," *J Biol Chem*, 274(45):32079-84 (1999), the contents of which are incorporated herein by reference in their entirety.

Masked Phosphoantigen



Compound 37

replacing compounds 21.1.2 and 6.2.0b with compound 37.1.



to give compound 37.3. Compound 37.3 may then be reacted with one

equivalent of 37.4 followed by an excess of 37.5 in the presence of base, in an inert solvent to give compound 37.6 after purification by chromatography.

Hydrogenation with palladium on carbon will give compound 37.7. Compound 37.7 may then be reacted with one equivalent of compound 37.8 in an inert

- 5 solvent with an agent such as triisopropylbenzenesulfonyl 3-nitro-1,2,4 triazole and base in an inert solvent. Reaction of the product in a similar fashion with (2-Hydroxy-ethoxy)-acetic acid allyl ester, followed by purification by chromatography, and removal of the allyl protecting group with Pd(0) will give compound 37.1.

10

Compound 37.5 may be prepared by treating acetic acid 3-methyl-4-oxo-butyl ester with pivalic acid anhydride and boron trifluoride etherate in an inert solvent and then hydrolyzing the acetate ester with aqueous sodium hydroxide.

15

Example 38

- Compound 38 is a multifunctional drug delivery vehicle with targeting ligands for urokinase, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1) and sigma receptors. The drug has a phosphatase activated time delay clock like trigger
- 20 that will unmask the intracellular transport ligand. The drug has an intracellular trigger that will be activated by thioreductases and will free an analog of wortmannin, which is an irreversible inhibitor of phosphatidylinositol 3-kinase. The covalent modification of phosphatidylinositol 3-kinase will generate neoantigens to which the patient may be sensitized so as to elicit a targeted
- 25 antitumor immunity. The following references relate to this subject matter:
- Creemer L.C., et al., "Synthesis and *in Vitro* Evaluation of New Wortmannin

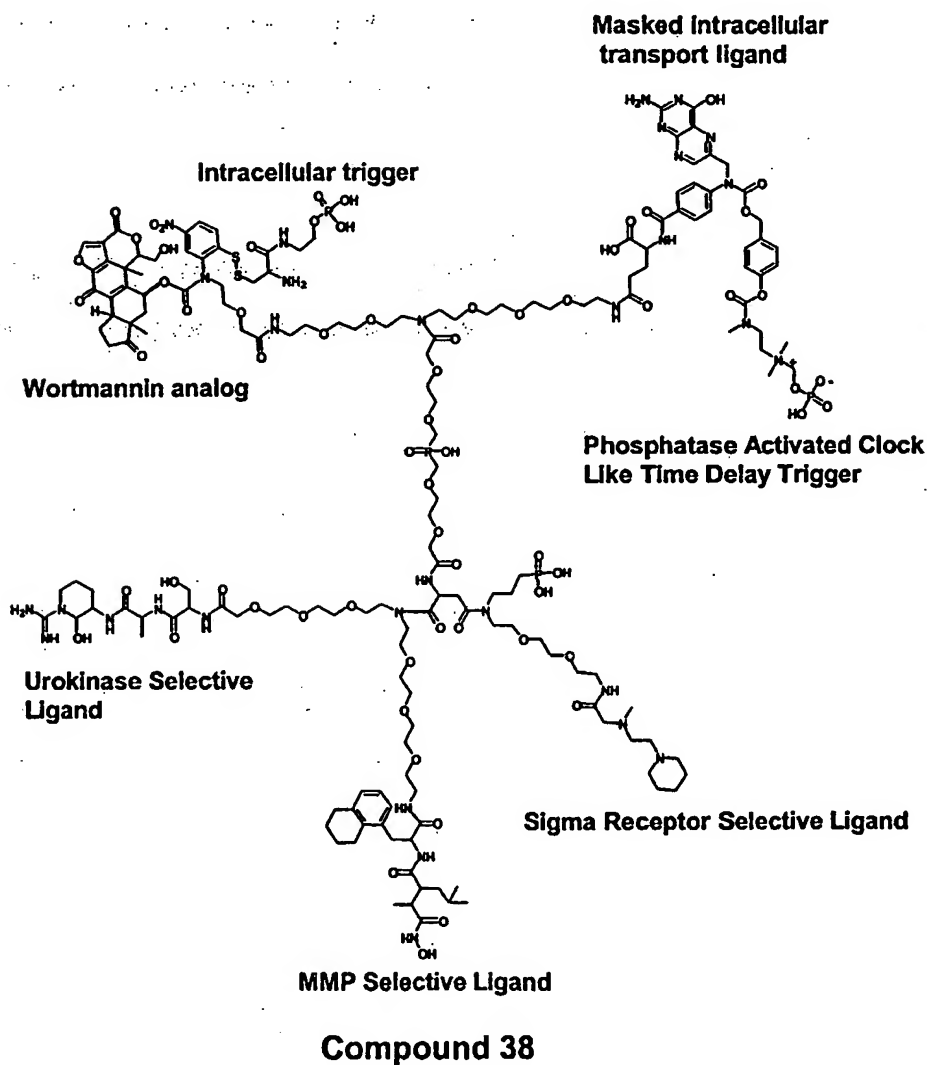
Esters: Potent Inhibitors of Phosphatidylinositol 3-Kinase," *J Med Chem*,

39:5021-5024 (1996); Wymann M.P., et al "Wortmannin Inactivates

Phosphoinositide 3-Kinase by Covalent Modification of Lys-802, A Residue

Involved in the Phosphate Transfer Reaction," *Mol Cell Biol*, 4:1722-33 (1996),

5 the contents of which are incorporated herein by reference in their entirety.

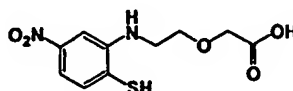


The chemical structure of compound 1 is a complex molecule. It features a fluoromethyl phosphonate group (Fm-O-P(=O)(Fm)-O-) linked to a chain containing an Fmoc-protected amine (Fmoc-NH-CH2-CH2-NH-C(=O)-). This chain is connected via a disulfide bridge (-S-S-) to a 4-nitrophenyl group (p-NO2-C6H4-). The 4-nitrophenyl group is further linked to a large, complex polycyclic aromatic system, which includes a naphthalene-like core with various substituents, including a methoxy group and a carbonyl group.

Compound 38.1 may be prepared by treating compound 38.2 with phosgene in an inert solvent, then reacting the chloroformate with compound 38.3, and then selectively removing the Bsm ester with tris(2-aminoethyl)amine under conditions that will leave the Fmoc groups intact. Compound 38.2 is a known compound.

752

Compound 38.3 may be prepared by the method described for the synthesis of compound 21.1.2b by replacing compound 17.11.1a with compound 38.4 in the synthetic scheme.



Compound 38.4

- 5 Compound 38.4 may be prepared by a multi-step procedure. Alkylation of 2-Fluoro-5-nitro-phenylamine with (2-Chloro-ethoxy)-acetic acid methyl ester in an inert solvent in the presence of base will give [2-(2-Fluoro-5-nitro-phenylamino)-ethoxy]-acetic acid methyl ester. Treatment with sodium sulfide, followed by hydrolysis of the methyl ester will give compound 38.4.

10

The neoantigens for sensitization may be obtained by reacting phosphoinositide 3-kinase with compound 38.2 or by employing synthetic oligopeptides with amino sequences that correspond to the modified site of the enzyme that have the wortmannin analog covalently attached in the appropriate manner.

15

Example 39

- Compound 39 is similar to compound 38, however the drug bears a tamoxifen analog that is linked to a masked alkylating group. The tamoxifen analog will be released and converted into an active alkylating agent upon activation of an intracellular trigger by thioreductases. The estrogen receptor will be alkylated at cysteine 530 and in the process neoantigens will be generated. P-glycoprotein will also be selectively alkylated. Accordingly, neoantigens derived from both the estrogen receptor and p-glycoprotein will be generated.
- 20

Neoantigens for sensitization may be prepared by treating estrogen receptor and p-glycoprotein with compound 39.2. Alternatively, synthetic oligopeptides that correspond to the modified portions of the respective proteins may be employed.

The following references relate to this subject matter: Katzenellenbogen J.A., et

- 5 al., "Efficient and Highly Selective Covalent Labeling of the Estrogen Receptor with [³H]Tamoxifen Aziridine," *J Biol Chem*, 258(6):3487-3495 (1983); Harlow

K.W., et al., "Identification of Cysteine 530 as the Covalent Attachment Site of an

Affinity-labeling Estrogen (Ketononestrol Aziridine) and Antiestrogen (Tamoxifen

Aziridine) in the Human Estrogen Receptor," *J Biol Chem*, 264(29):17476-17485

- 10 (1989); Reese J.C.; Katzenellenbogen B.S., "Mutagenesis of Cysteines in the

Hormone Binding Domain of the Human Estrogen Receptor," 266(17):10880-

10887 (1991); Aliau S., et al., "Cysteine 530 of the Human Estrogen Receptor α

Is the Main Covalent Attachment Site of 11 β -(Aziridinylalkoxyphenyl)estradiols,"

Biochemistry, 38:14752-14762 (1999); Robertson D.W., et al., "Tamoxifen

- 15 Aziridines: Effective Inactivators of the Estrogen Receptor," *Endocrinology*,

109(4):1298-300 (1981); Safa A.R., et al., "Tamoxifen Aziridine, a Novel Affinity

Probe for P-glycoprotein in Multidrug Resistant Cells," *Biochem Biophys Res*

Commun, 202(1):606-12 (1994), the contents of which are incorporated herein

by reference in their entirety.

Estrogen Receptor and P-Glycoprotein
Binding Ligand

Masked intracellular
transport ligand

Masked alkylating group

Intracellular trigger

Phosphatase Activated Clock
Like Time Delay Trigger

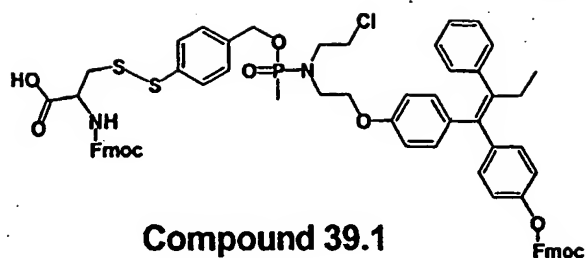
Urokinase Selective
Ligand

Sigma Receptor Selective Ligand

MMP Selective Ligand

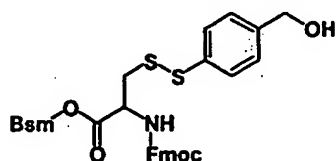
Compound 39

Compound 39 may be prepared by the methods described for compound 38 by
5 replacing compound 38.1 with compound 39.1.

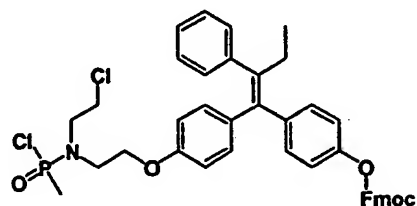


Compound 39.1

Compound 39.1 may be prepared by reacting compound 36.5 and compound 39.2 in an inert solvent in the presence of base and then selectively cleaving the Bsm ester with tris(2-aminoethyl)amine under conditions that will leave the Fmoc groups intact.

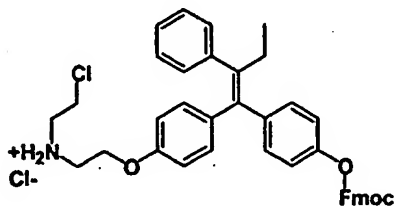


Compound 36.5

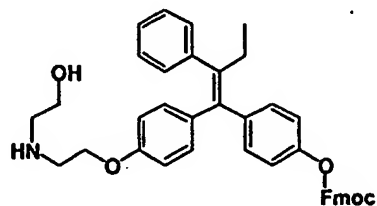


Compound 39.2

Compound 39.2 may be prepared by treating compound 39.3 with methylphosphonic acid dichloride and base in an inert solvent. Compound 39.3 may be prepared by treating compound 39.4 with HCl or thionyl chloride in an inert solvent.



Compound 39.3

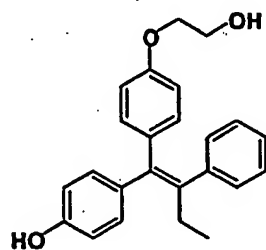


Compound 39.4

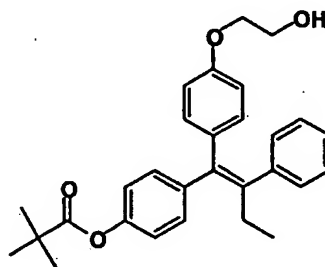
Compound 39.4 may be made by a multi-step process. Treatment of 2-[2-(4-Bromo-phenoxy)-ethoxy]-tetrahydro-pyran with n-butyl lithium in an inert solvent followed by reaction with 2-Phenyl-1-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-butan-1-one and HCl treatment will give compound 39.5. The following references

5 relate to this subject matter: Katzenellenbogen J.A., et al., "Efficient and Highly Selective Covalent Labeling of the Estrogen Receptor with [^3H]Tamoxifen Aziridine," *J Biol Chem*, 258(6):3487-3495 (1983), the contents of which are incorporated herein by reference in their entirety.

10 Treatment with sodium hydride and pivaloyl chloride in an inert solvent will give compound 39.6.



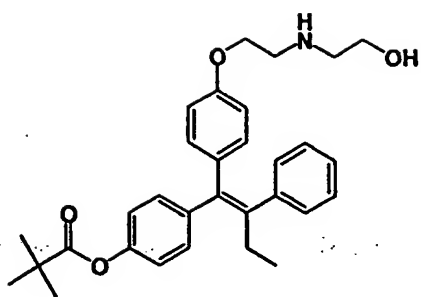
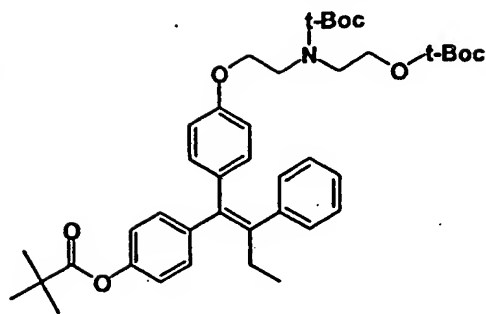
Compound 39.5



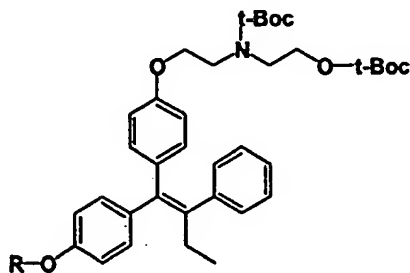
Compound 39.6

Treatment with tosyl chloride and base in an inert solvent will give the tosylate

15 that may then be reacted with ethanolamine to give compound 39.7. Treatment with di-t-butyl pyrocarbonate and in an inert solvent with a base will give compound 39.8.

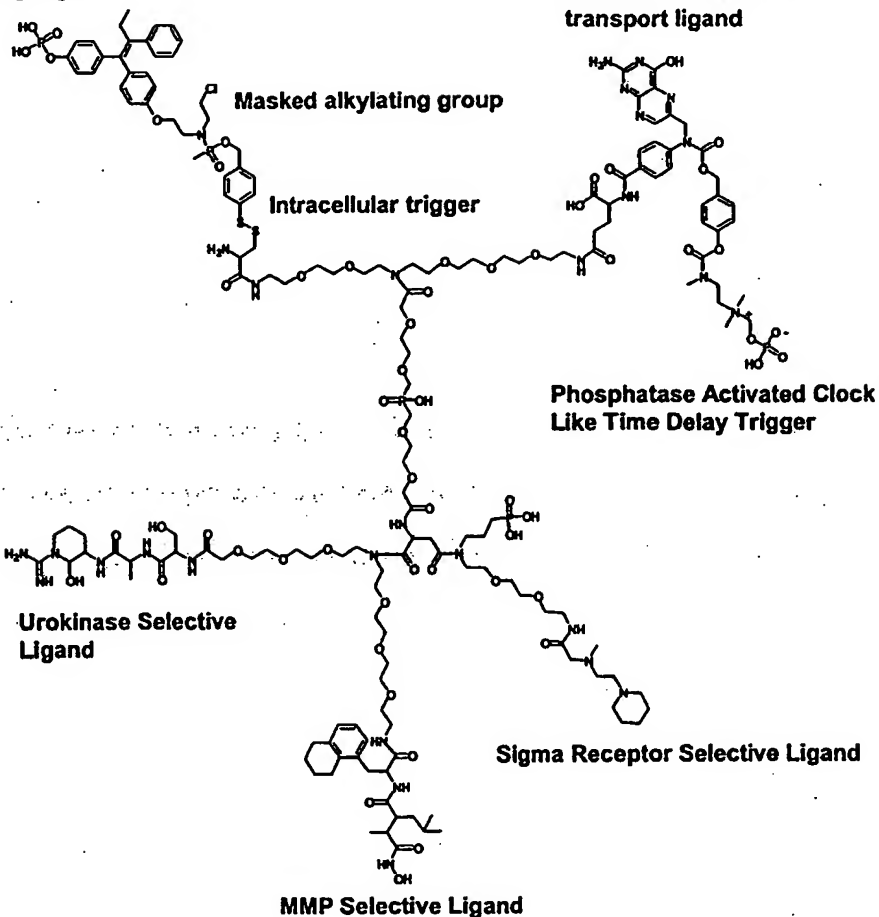
**Compound 39.7****Compound 39.8**

- Alkaline hydrolysis of compound 39.8 will selectively cleave the pivaloyl ester and give compound 39.9a. Treatment with 9-fluorenylmethyl chloroformate, in
5 an inert solvent with base, will then give compound 39.9b. Removing the t-Boc groups with acid will give compound 39.4.

**Compound 39.9a** R = H**Compound 39.9b** R = Fmoc

10 Example 40

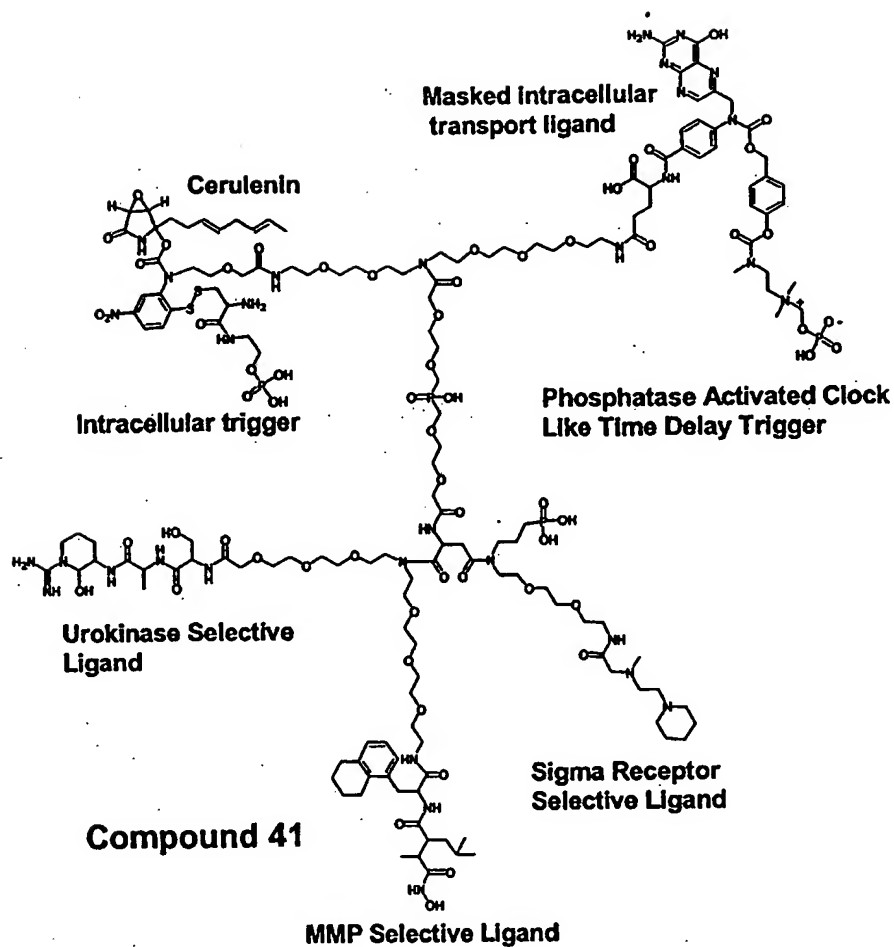
Compound 40 is similar to compound 39, however, the tamoxifen analog has a phosphate group to increase solubility. The phosphate group will be cleaved by esterases to generate a ligand with binding affinity to the estrogen receptor.

**Estrogen Receptor and P-Glycoprotein
Binding Ligand****Masked intracellular
transport ligand****Compound 40**

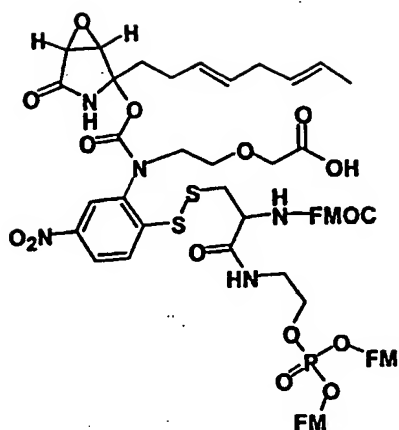
Compound 40 may be prepared by the method described for compound 39 by
 5 reacting compound 39.9a with phosphorochloridic acid bis-(9H-fluoren-9-
 ylmethyl) ester and a base such as triethylamine in an inert solvent (in the place
 of Fmoc chloroformate).

Example 41

Compound 41 is similar to compound 38, however, the drug will deliver cerulenin, an irreversible inhibitor of fatty acid synthase. The interaction of cerulenin and fatty acid synthase will generate neoantigens in a targeted manner. The following references relate to this subject matter: Funabashi H., et
5 al., "Binding Site of Cerulenin in Fatty Acid Synthetase," *J Biochem*, 105:751-755 (1989); Moche M., et al., "Structure of the Complex between the Antibiotic Cerulenin and Its Target, β -Ketoacyl-Acyl Carrier Protein Synthase," *J Biological Chem*, 274(10):6031-6034 (1999), the contents of which are incorporated herein by reference in their entirety.



Compound 41 may be prepared by the method described for compound 38 by replacing compound 41.1 for compound 38.1.

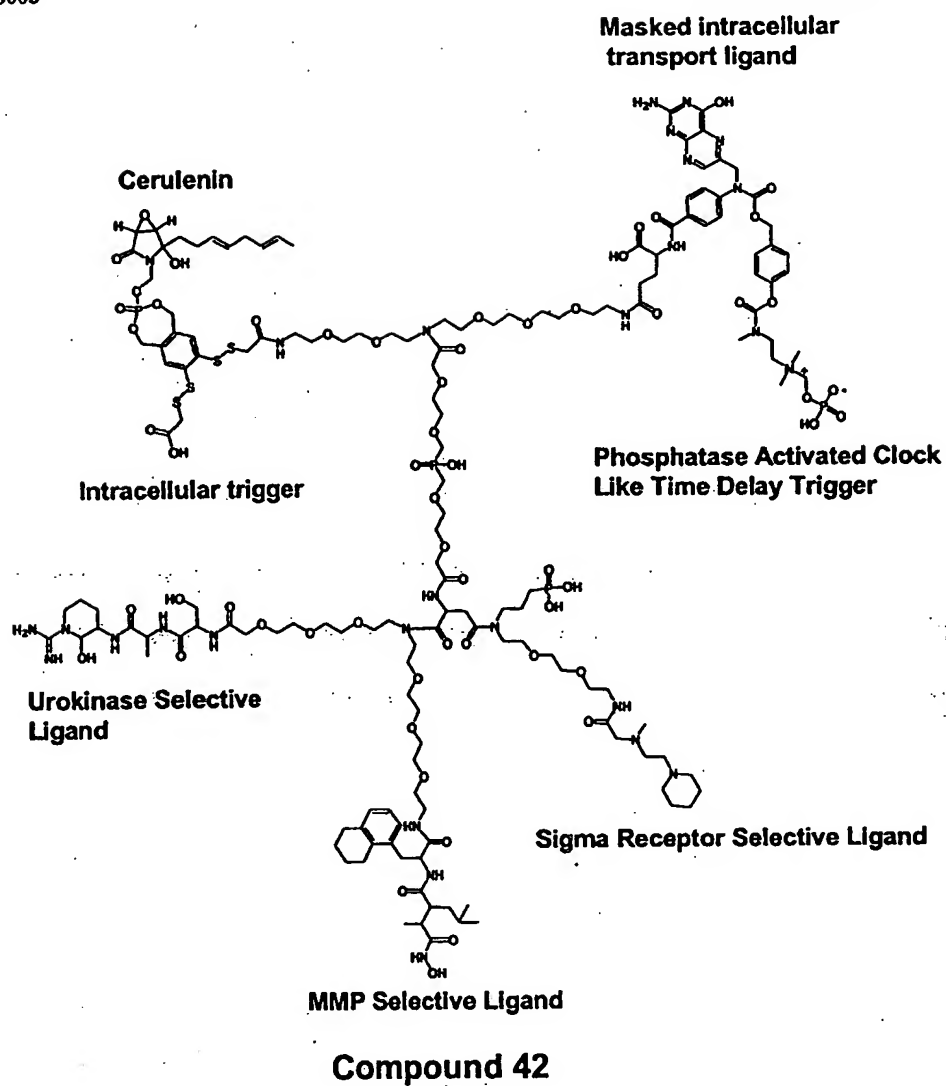


Compound 41.1

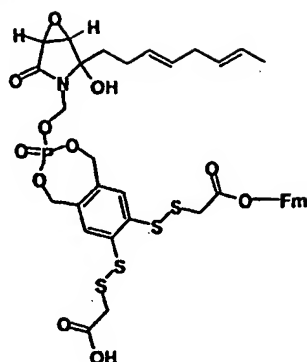
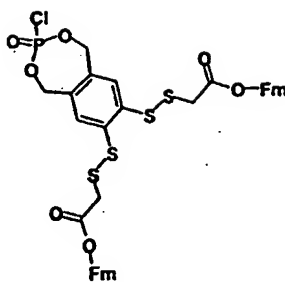
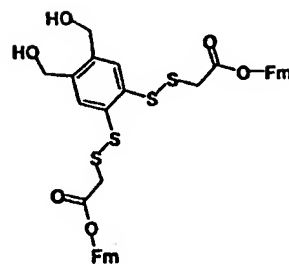
Compound 41.1 may be prepared by reacting compound 38.3 with phosgene in an inert solvent, then reacting the product with cerulenin in the presence of a base, and then selectively removing the Bsm ester with tris(2-aminoethyl)amine under conditions that will leave the Fmoc groups intact.

Example 42

Compound 42 is similar to compound 41, however, a different trigger is used to release the cerulenin. The trigger will be activated by thioreductases, which will free the n-methyl-phosphate derivative of cerulenin, which will be degraded by phosphatase to cerulenin.



Compound 42 may be prepared by the method described for compound 38 by replacing compound 38.1 with compound 42.1.

**Compound 42.1****Compound 42.2****Compound 42.3**

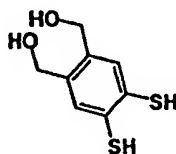
Compound 42.1 may be prepared by a multi-step process. Reacting cerulenin with formaldehyde in an inert solvent, then reacting the n-hydroxymethylated product with compound 42.2 in the presence of base, and then treating with one equivalent of strong base, will give compound 42.1 after purification by chromatography. The following references relate to this subject matter:

Bundgaard H., "Formation of Prodrugs of Amines, Amides, Ureides, and Imides," *Methods in Enzymology*, 112:347-359 (1985), the contents of which are incorporated herein by reference in their entirety.

10

Compound 42.2 may be prepared by reacting compound 42.3 with phosphorous oxychloride in an inert solvent in the presence of base. Compound 42.3 may be prepared by reacting mercapto-acetic acid 9H-fluoren-9-ylmethyl ester with diethyl azidocarboxylate in an inert solvent and then reacting the product with

15 compound 42.4.

**Compound 42.4**

Compound 42.4 may be prepared by a multi-step process. Reacting 4,5-Dichloro-phthalic acid with sodium ethanethiolate in dimethylformamide will give 4,5-dimercapto-phthalic acid. Reduction with borane in a solvent such as tetrahydrofuran will give compound 42.4. The following references relate to this subject matter: Testaferri L., et al., "Simple Syntheses of Aryl Alkyl Thioethers and of Aromatic Thiols from Unactivated Aryl Halides and Efficient Methods for Selective Dealkylation of Aryl Alkyl Ethers and Thioethers," *Synthesis*, 751-755 (1983), the contents of which are incorporated herein by reference in their entirety.

10

Neoantigens for sensitization may be prepared by treating fatty acid synthase with cerulenin. Alternatively, synthetic oligopeptides that correspond to the modified portions of the fatty acid synthase may be employed.

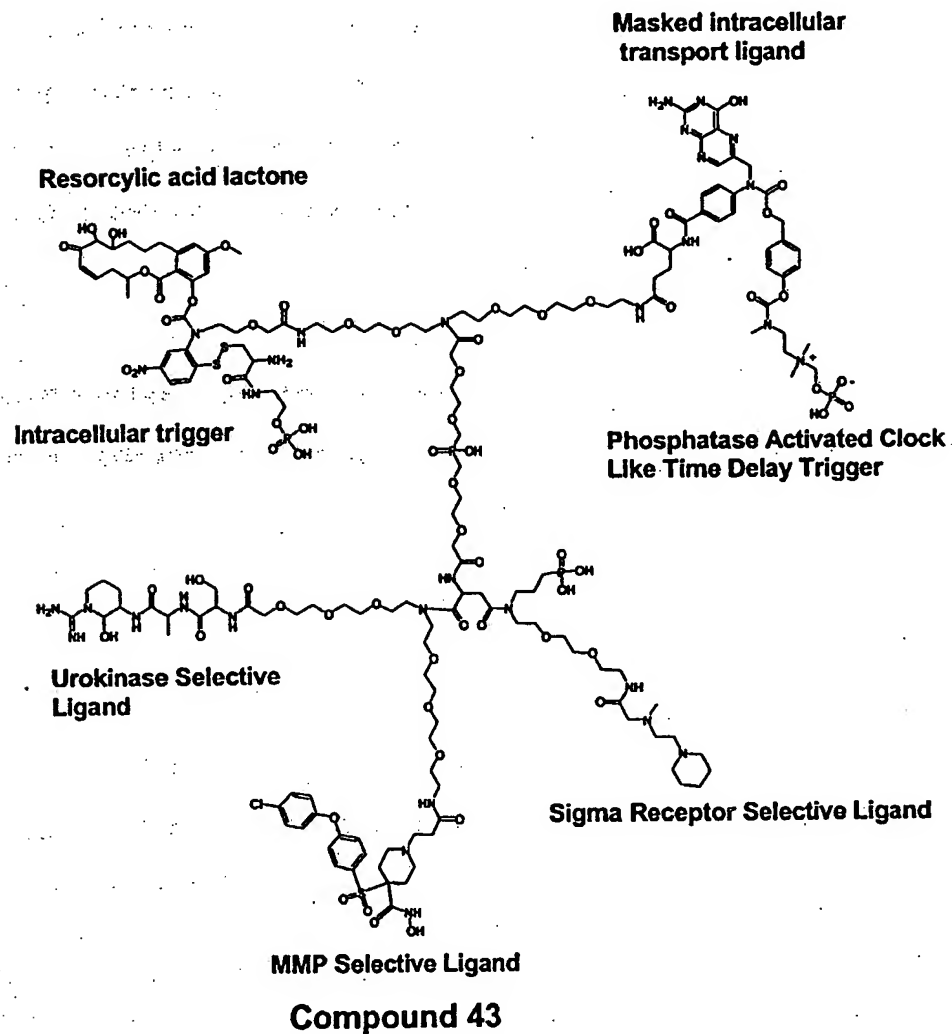
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Example 43

Compound 43 is a multifunctional drug delivery vehicle with targeting ligands for urokinase, MMPs 2, 3, 9, 12, and 13, and sigma receptors. The drug has a masked intracellular transporter with a phosphatase activated time delay clock like trigger and will release resorcylic acid lactone upon activation of an intracellular trigger by thioreductase. Resorcylic acid lactone is a potent irreversible inhibitor of MEK. The interaction of resorcylic acid lactone and MEK will generate neoantigens that may be used in the method of targeted immunotherapy. The following references relate to this subject matter: Zhao A., et al., "Resorcylic Acid Lactones: Naturally Occurring Potent and Selective Inhibitors of MEK," *J Antibiotics*, 52(12):1086-1094 (1999); Hoshino R., et al.,

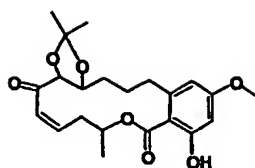
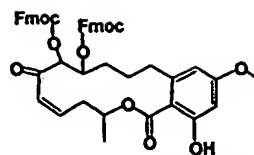
25

"Constitutive Activation of the 41-/43-kDa Mitogen-activated Protein Kinase Signaling Pathway in Human Tumors," *Oncogene*, 18:813-822 (1999), the contents of which are incorporated herein by reference in their entirety.



5

Compound 43 may be prepared by the methods described for compound 38 by replacing compound 38.2 with compound 43.1a or compound 43.1b and also by replacing compound 21.2.1d with compound 18.1.

**Compound 43.1a****Compound 43.1b**

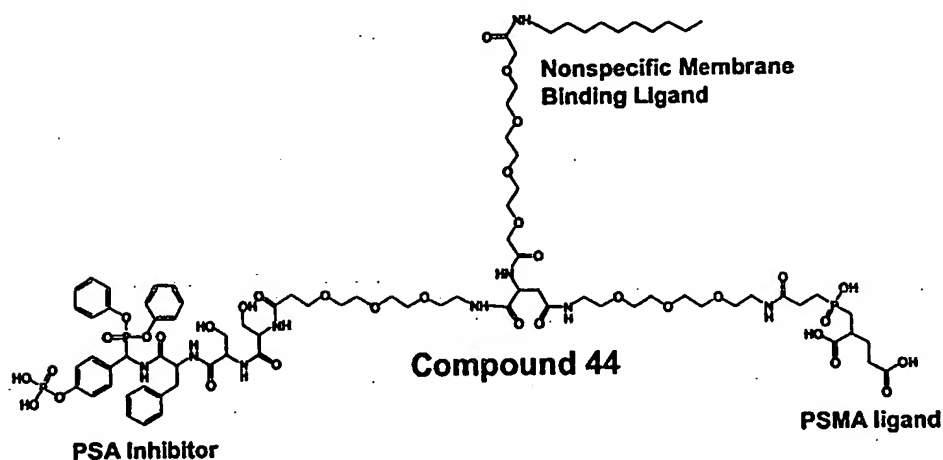
Compound 43.1a may be prepared by routine methods of acetonide formation
5 from resorcylic acid lactone. The following references relate to this subject
matter: Greene, Theodora W.; Wuts, Peter G.M. (1999) "Protective Groups in
Organic Synthesis" John Wiley & Sons, Inc. p 207-213, the contents of which are
incorporated herein by reference in their entirety.

10 Compound 43.1b may be prepared by treating compound 43.1a with (1,1-Dioxo-
1H-1λ6-benzo[b]thiophen-2-yl)-methyl chloroformate and base in an inert
solvent, then treating with acid to cleave the acetonide protecting group, then
treating with 9H-fluoren-9-ylmethyl chloroformate in the presence of a base, and
then selectively removing the Bsmoc group with tris(2-aminoethyl)amine under
15 conditions that will leave the Fmoc group intact.

The neoantigens for sensitization purposes may be prepared by treating MEK
with resorcylic acid lactone. Alternatively, synthetic oligopeptides that
correspond to the modified MEK with resorcylic acid lactone covalently attached
20 may be employed.

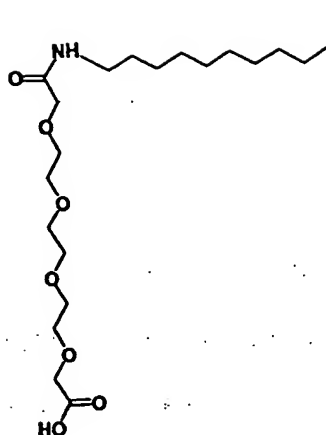
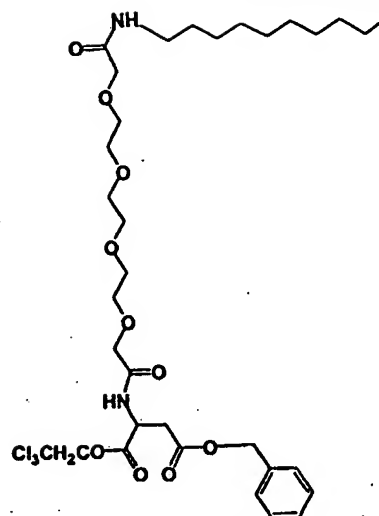
Example 44

Compound 44 is a multifunctional drug delivery vehicle with a targeting ligand for prostatic specific membrane antigen, a nonspecific targeting ligand for cell membranes, and an irreversible inhibitor for prostate specific antigen. The interaction of the PSA inhibitor and PSA will generate neoantigens for use with the method of targeted neoantigen immunotherapy. The role of the nonspecific membrane binding ligand is to enhance the affinity of the drug for PSMA positive cells. The PSMA binding ligand will bind with a K_i in the low nanomolar range to PSMA. The additional binding energy provided by the membrane binding ligand to the cell should provide for essentially irreversible binding to PSMA positive cells.

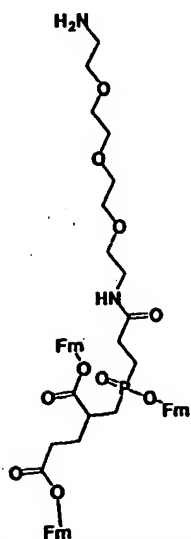
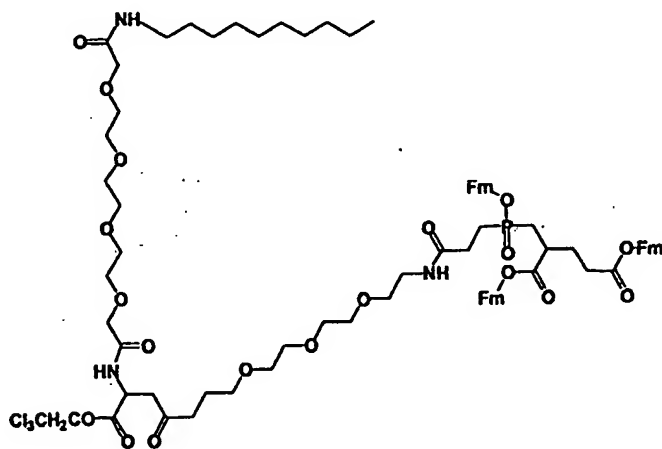


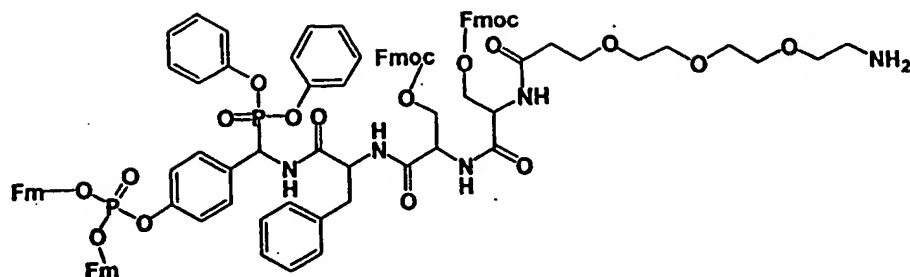
15

Compound 44 may be prepared by a multi-step process. Coupling L- aspartic acid α 2,2,2 trichloroethyl β benzyl diester with compound 44.1 in an inert solvent will give compound 44.2.

**Compound 44.1****Compound 44.2**

Removal of the benzyl group by catalytic hydrogenation with Pd on carbon and coupling to compound 44.3 will give compound 44.4.

**Compound 44.3****Compound 44.4**



Compound 44.5

Compound 44.4 may be treated with Zn and acid to cleave the 2,2,2 trichloroethyl ester. The product may then be coupled with compound 44.5.

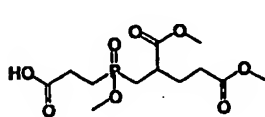
Treatment of the product with base will remove the Fmoc and cleave the Fm

5 ester groups and give compound 44.

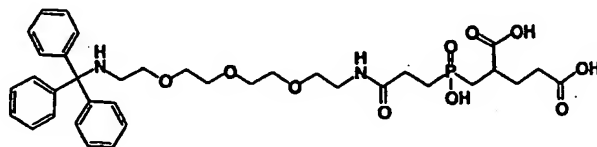
Compound 44.1 may be prepared by coupling {2-[2-(2-Carboxymethoxy-ethoxy)-ethoxy]-ethoxy}-acetic acid with decylamine and isolating the monosubstituted product.

10

Compound 44.3 may be prepared by a multi-step process. Coupling 2-(2-[2-(2-(Trityl-amino)-ethoxy)-ethoxy]-ethoxy)-ethylamine and compound 6.6.1 followed by alkaline hydrolysis will give compound 44.3b.



Compound 6.6.1



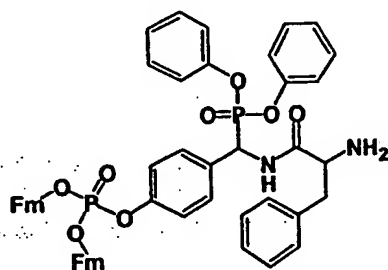
Compound 44.3b

15

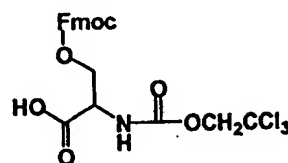
Compound 44.3b may be esterified with (9H-Fluoren-9-yl)-methanol and a condensing agent such as dicyclohexylcarbodiimide or triisopropylbenzenesulfonyl 3-nitro-1,2,4 triazole and base in an inert solvent.

Treatment with HCL will remove the trityl protecting group and give compound 44.3 as the hydrochloride salt.

Compound 44.5 may be prepared by a multi-step process.



Compound 44.5a



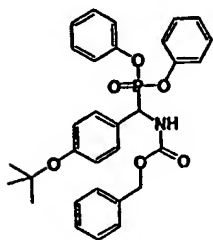
Compound 44.5b

5

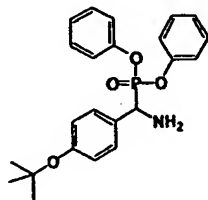
Compound 44.5a may be coupled with compound 44.5b. The product may be treated with Zn and acid to remove the 2,2,2 trichloroethyl group and the product may again be coupled with compound 44.5b. Treatment with Zn and acid followed by coupling to 3-(2-{2-[2-(2,2,2-Trichloro-ethoxycarbonylamino)-ethoxy]-ethoxy}-ethoxy)-propionic acid and removal of the trichloro-ethoxycarbonyl protecting group with Zn and acid will give compound 44.5.

10

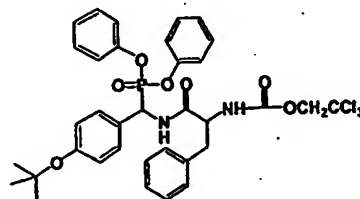
Compound 44.5a may be prepared by a multi-step process.



Compound 44.5c



Compound 44.5d



Compound 44.5e

15

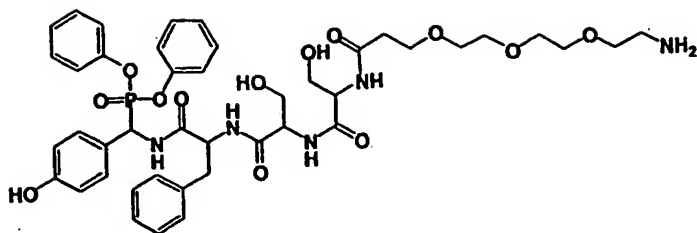
Reacting 4-tert-butoxy-benzaldehyde, benzyl carbamate, triphenyl phosphite, and glacial acetic acid will give compound 44.5c. Catalytic hydrogenation with Pd on carbon in methanol with HCL will give compound 44.5d. The following references relate to this subject matter: Oleksyszyn J., et al., "Novel Amidine-Containing Peptidyl Phosphonates as Irreversible Inhibitors for Blood Coagulation and Related Serine Proteases," *J Med Chem*, 37:226-231 (1994); Oleksyszyn J., et al., "Diphenyl 1-Aminoalkanephosphonates," *Synthesis*, 985-986 (1979), the contents of which are incorporated herein by reference in their entirety.

10

Coupling to L- N-2,2,2 trichloroethoxycarbonyl phenylalanine will give compound 44.5e. Treatment with trifluoroacetic acid will remove the t-butyl group. Treatment of the product with phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester and a base such as triethylamine in an inert solvent, followed by removal of the 2,2,2 trichloroethylcarbonyl protecting group with Zn and acid will give compound 44.5a.

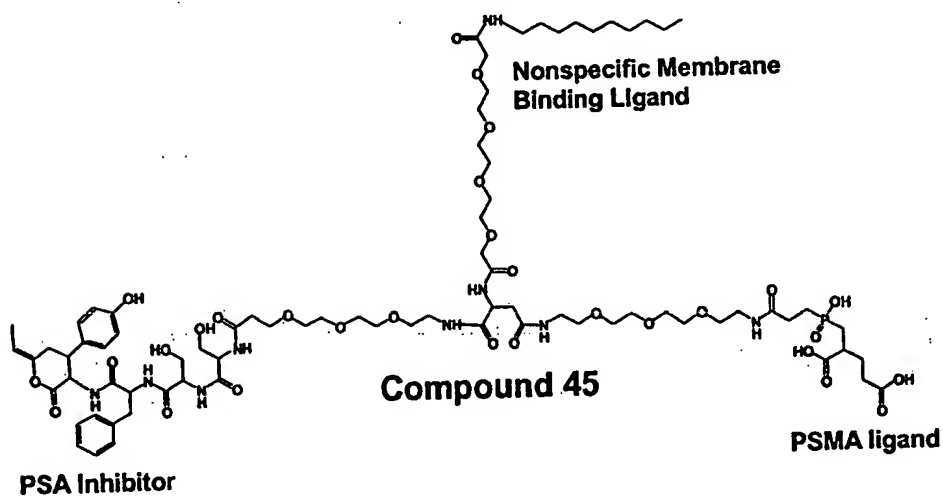
The neoantigen for sensitization purposes may be prepared by treating PSA with compound 44.6. Alternatively, synthetic oligopeptides that correspond to the modified amino acid sequence of PSA with the inhibitor covalently attached may be employed.

20

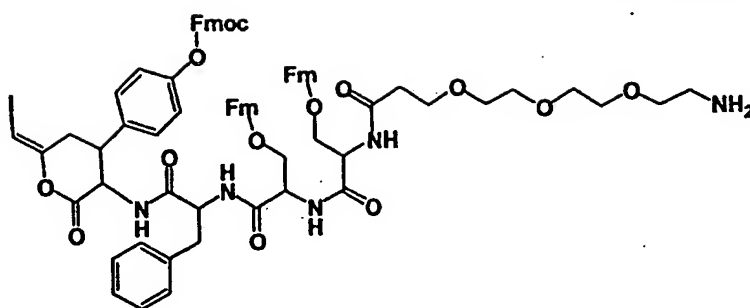
**Compound 44.6****Example 45**

Compound 45 is similar to compound 44. However, in compound 45 a haolenol

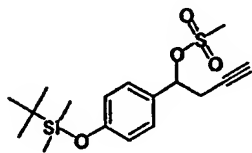
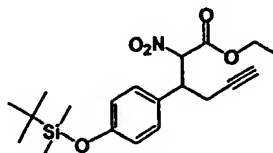
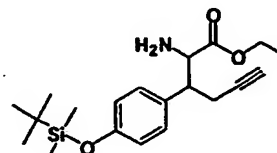
- 5 lactone based inhibitor is used to covalently modify PSA and generate neoantigens.

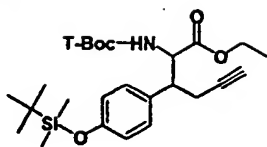
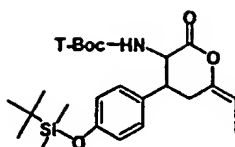
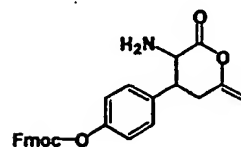


- 10 Compound 45 may be prepared by the method described for compound 44 by replacing compound 44.5 with compound 45.1.

**Compound 45.1**

Compound 45.1 may be prepared by a multi-step procedure. Reacting ethyl
 nitroacetate and compound 45.2 in an inert solvent in the presence of a base
 such as sodium hydride will give compound 45.3. The following references
 relate to this subject matter: Sofia M.J.; Katzenellenbogen J.A., "Enol Lactone
 Inhibitors of Serine Proteases. The Effect of Regiochemistry on the Inactivation
 Behavior of Phenyl-Substituted (Halomethylene)tetra- and -dihydrofuranones
 and (Halomethylene)tetrahydropyranones toward α -Chymotrypsin: Stable Acyl
 Enzyme Intermediate," *J Med Chem*, 29:230-238 (1986); Luger P., et al.,
 "Carbinols, Carbamates et esters Propynyliques, et Leur Activit Hypnotique,"
Helv Chim Acta, 42:2379-2393 (1959), the contents of which are incorporated
 herein by reference in their entirety.

**Compound 45.2****Compound 45.3****Compound 45.4**

**Compound 45.5****Compound 45.6****Compound 45.7**

Selective reduction of the nitro group by a reagent such as

diethylchlorophosphite will give compound 45.4. The following references relate

5 to this subject matter: Fischer B.; Sheihet L., "Diethyl Chlorophosphite: A Mild

Reagent for Efficient Reduction of Nitro Compounds to Amines," *J Org Chem*,

63:393-395 (1998), the contents of which are incorporated herein by reference in

their entirety.

10 Treatment with di-*t*-butyl pyrocarbonate and in an inert solvent will give
compound 45.5.

In an alternate method, the free acid derivative of compound 45.5 may be

prepared by reacting compound 45.2 and 2-*tert*-Butoxycarbonylamino-malonic

15 acid dimethyl ester in the presence of a strong base, the hydrolyzing the methyl
esters, and heating to decarboxylate. The following references relate to this

subject matter: Rai R. ; Katzenellenbogen J.A., "Effect of Conformational

Mobility and Hydrogen-Bonding Interactions on the Selectivity of Some

Guanidinoaryl-Substituted Mechanism-Based Inhibitors of Trypsin-like Serine

20 Proteases," *J Med Chem*, 35:4297-4305 (1992), the contents of which are

incorporated herein by reference in their entirety.

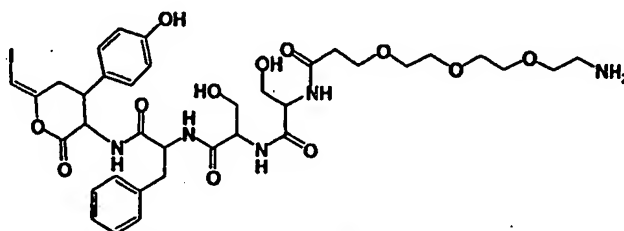
Hydrolysis of the methyl ester of compound 45.5 followed by treatment with iodine in an inert solvent will give compound 45.6. Treatment with tetrabutylammonium fluoride or acid will remove the t-butyldimethylsilyl protecting group. Treatment with 9-fluorenylmethyl chloroformate and base in an inert solvent followed by acid treatment will give compound 45.7.

Compound 45.7 may be coupled with t-Boc L-phenylalanine. The product may be treated with acid to remove the t-Boc group and then may be coupled with N-t-Boc, O-Fmoc-L-serine (L-2-tert-Butoxycarbonylamino-3-(9H-fluoren-9-ylmethoxycarbonyloxy)-propionic acid). The t-Boc group may again be removed and the product may then be coupled to another N-Boc-O-Fmoc-L-serine. Removal of the t-Boc group, followed by coupling to 3-{2-[2-(2-tert-butoxycarbonylamino-ethoxy)-ethoxy]-ethoxy}-propionic acid, followed by removal of the t-Boc group will give compound 45.1.

15

The neoantigen for sensitization purposes may be prepared by treating PSA with a compound such as compound 45.8. Alternatively, synthetic oligopeptides that correspond to the modified amino acid sequence of PSA with the inhibitor covalently attached may be employed.

20

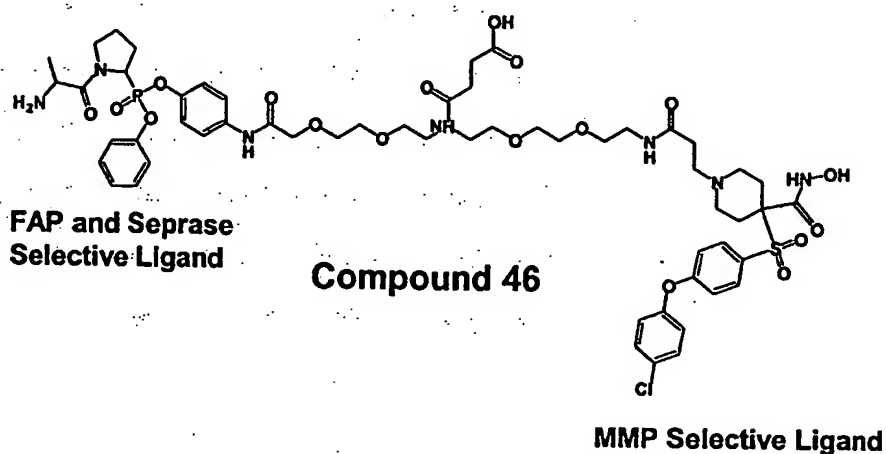


Compound 45.8

Example 46

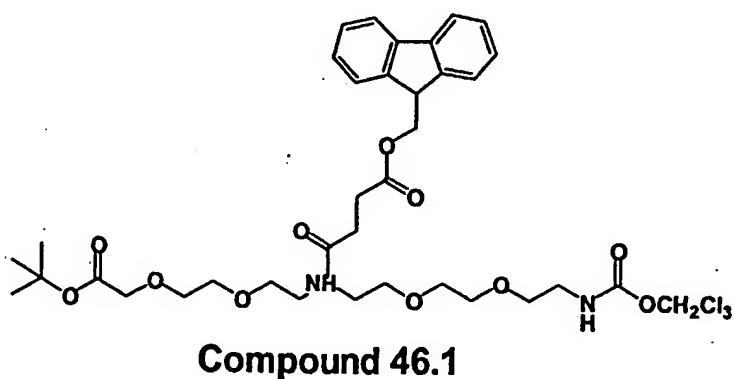
Compound 46 has targeting ligands for MMPs 2, 3, 9, 12, and 13, Fibroblast Activation Protein (FAP), and Seprase. The drug will bind irreversibly to FAP and seprase and generate neoantigens that may be used for targeted

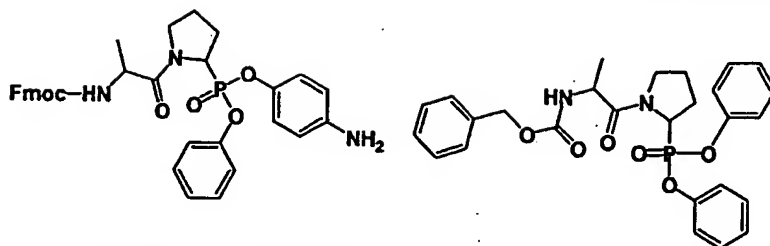
5 immunotherapy.



Compound 46 may be prepared by a multistep process. Coupling compound

10 17.7 with succinic acid mono-(9H-fluoren-9-ylmethyl) ester will give compound 46.1.



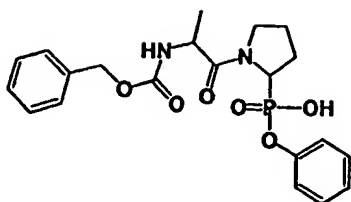
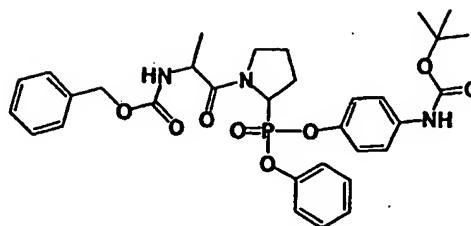


Compound 46.2 Compound 46.3

Treatment with trifluoroacetic acid will cleave the t-butyl ester group. The product may then be coupled to compound 46.2. Treatment with Zn and acid will cleave the 2,2,2 trichloroethoxycarbonyl group. The product may then be coupled to compound 18.1. Treatment with base will remove the protecting groups and give compound 46.

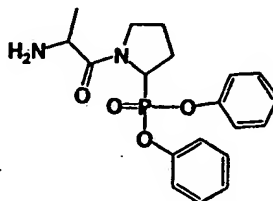
Compound 46.2 may be prepared by a multi-step process. Treating compound 46.3 with sodium hydroxide will give compound 46.4. The following references relate to this subject matter: Belyaev A., et al., "Structure-Activity Relationship of Diaryl Phosphonate Esters as Potent Irreversible Dipeptidyl Peptidase IV Inhibitors," *J Med Chem*, 42:1041-1052 (1999); Belyaev A., et al., "A New Synthetic Method for Proline Diphenyl Phosphonates," *Tetrahedron Let*, 36(21):3755-3758 (1995), the contents of which are incorporated herein by reference in their entirety.

Esterification with (4-hydroxy-phenyl)-carbamic acid tert-butyl ester using a reagent such as as triisopropyl-benzenesulfonyl 3-nitro-1,2,4 triazole and base in an inert solvent will give compound 46.5.

**Compound 46.4****Compound 46.5**

- Catalytic hydrogenation with Pd on carbon, followed by treatment with 9H-
- 5 fluoren-9-ylmethyl chloroformate in the presence of a base such as pyridine in an inert solvent, followed by treatment with acid to remove the t-Boc group will give compound 46.2.

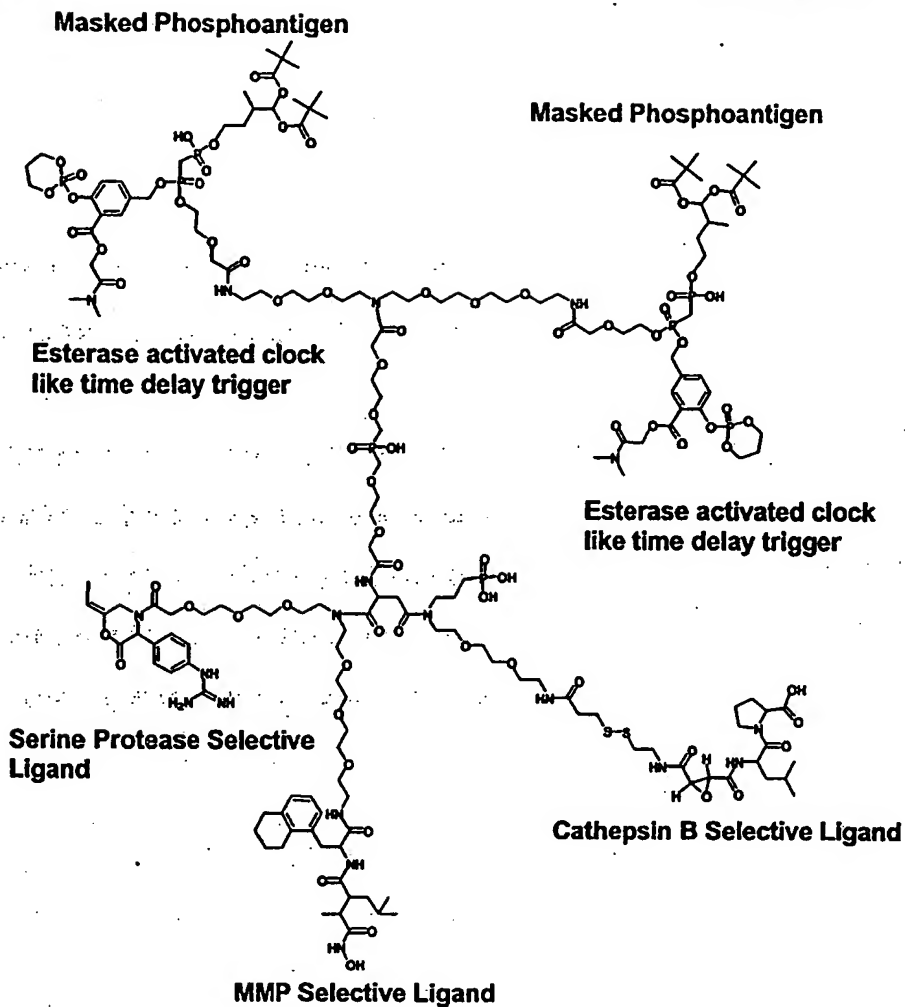
- The neoantigens for sensitization purposes may be prepared by treating FAP
- 10 and seprase with an inhibitor such as compound 46.6 Alternatively, synthetic oligopeptides that correspond to the modified portion of FAP and seprase with the inhibitor covalently attached may be employed.

**Compound 46.6**

15 Example 47

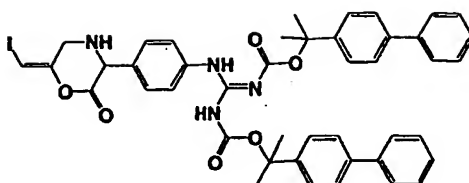
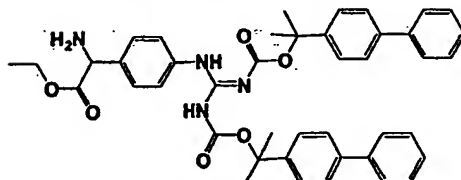
Compound 47 is a multifunctional drug delivery vehicle with targeting ligands for serine proteases, matrix metalloproteinases (1, 2, 3, 9, and MT-MMP-1), and cathepsin B. The compound is similar to compound 37, but has a haloenol

lactone derivative that is expected to irreversibly inactivate and, in the process, generate neoantigens from a variety of trypsin like serine proteases. This compound may be used for the method of targeted neoantigen generation where the neoantigens are derived from cathepsin B, urokinase, plasmin tissue plasminogen activator, trypsin, and human glandular kallikrein 2. Compound 47 also has two masked formyl butyl pyrophosphate analogs. 3-formyl -1-butyl-pyrophosphate and related derivatives are extremely potent activators of γ/δ T cells. The formyl groups will be unmasked by the action of esterase. The pyrophosphate analog will be unmasked by an esterase activated clock like trigger that will have a half life of about 90 minutes. Synergy between the innate and adaptive immune response is expected to augment the antitumor immune response. The following references relate to this subject matter: Rai R. ; Katzenellenbogen J.A., "Guanidinophenyl-Substituted Enol Lactones as Selective, Mechanism-Based Inhibitors of Trypsin-like Serine Proteases," *J Med Chem*, 35:4150-4159 (1992), the contents of which are incorporated herein by reference in their entirety.

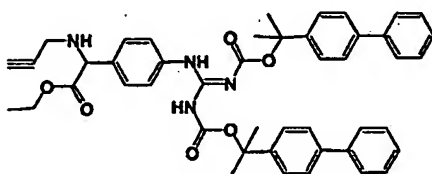
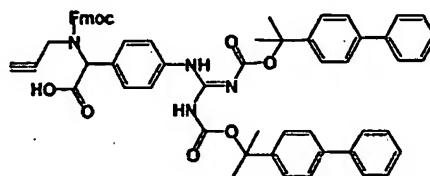


Compound 47

Compound 47 may be prepared by the method described for compound 37 by replacing compound 21.2.1b with compound 47.1.

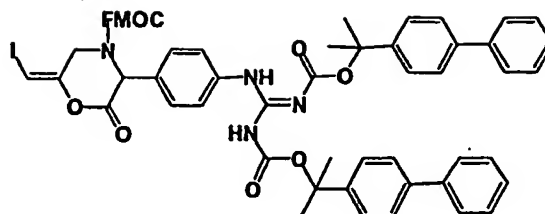
**Compound 47.1****Compound 47.2**

Compound 47.1 may be prepared by a multi-step process. Alkylating compound 47.2 with 3-Bromo-propyne in the presence of base in an inert solvent will give compound 47.3. Hydrolysis of the ethyl ester followed by treatment with 9H-fluoren-9-ylmethyl chloroformate in the presence of a base such as pyridine in an inert solvent will give compound 47.4.

**Compound 47.3****Compound 47.4**

10

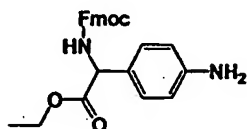
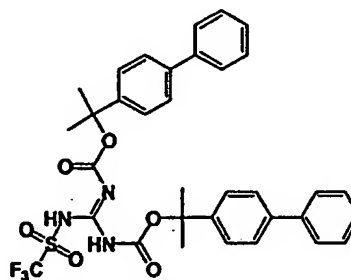
Treatment of compound 47.4 with iodine will give compound 47.5.

**Compound 47.5**

Treatment with base will give compound 47.1.

Compound 47.2 may be prepared by a multi-step process. P- amino-L- phenyl

- 5 glycine ethyl ester may be treated with 9H-fluoren-9-ylmethyl chloroformate in the presence of a base to give compound 47.6. Treatment with compound 47.7 in the presence of base in an inert solvent, followed by removal of the Fmoc group with base, will give compound 47.2.

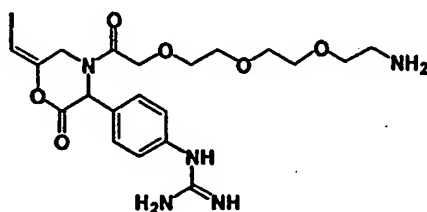
**Compound 47.6****Compound 47.7**

10

Compound 47.7 may be prepared by treating guanidine with a strong base and a reagent such as 4-(1-Biphenyl-4-yl-1-methyl-ethoxycarbonyloxy)-benzoic acid methyl ester followed by treatment with a base such as sodium hydride and triflic anhydride. The following references relate to this subject matter: Feichtinger K., et al., "Diprotected Triflylguanidines: A New Class of Guanidinylation Reagents," *J Org Chem*, 63:3804-3805 (1998), the contents of which are incorporated herein by reference in their entirety.

15

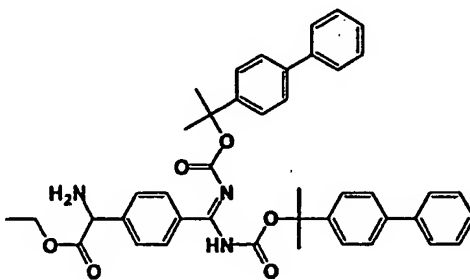
The neoantigens for sensitization purposes may be prepared by treating the respective serine proteases with an inhibitor such as compound 47.8 (as the dihydrochloride salt). Alternatively, synthetic oligopeptides that correspond to the modified portion of the proteases with the inhibitor covalently attached may be employed.



Compound 47.8

10 Example 48

Compound 48 is similar to compound 47, however the enol lactone inhibitor has a para amidino group rather than a para guanidino group. Compound 48 may be prepared by replacing compound 47.2 with compound 48.1 in the method described for compound 47.

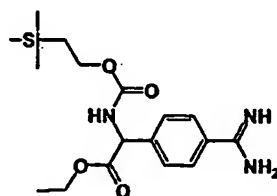


Compound 48.1

15

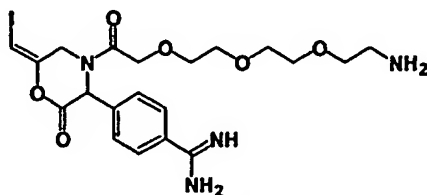
Compound 48.1 may be prepared by a multi-step process. Treating L- p-amidino phenylglycine ethyl ester with one equivalent of carbonic acid 4-nitro-phenyl ester 2-trimethylsilanyl-ethyl ester and base in an inert solvent will give after purification compound 48.2.

5

**Compound 48.2**

Treating compound 48.2 with base and a reagent such as 4-(1-Biphenyl-4-yl-1-methyl-ethoxycarbonyloxy)-benzoic acid methyl ester in an inert solvent and then
10 removing the silyl based protecting group with tetra-butylammonium fluoride will give compound 48.1.

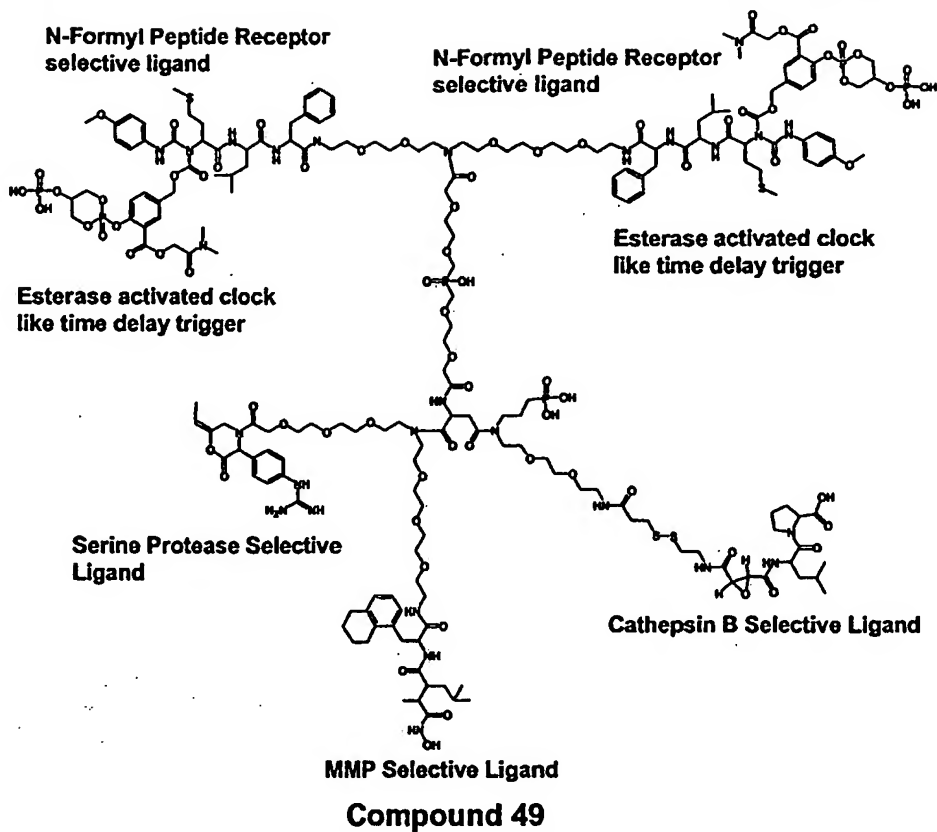
Neoantigens for sensitization purposes may be prepared by reacting the respective proteases with an inhibitor such as compound 48.3 (as the
15 dihydrochloride salt). Alternatively, synthetic oligopeptides that correspond to the modified portion of the proteases with the inhibitor covalently attached may be employed.

**Compound 48.3**

Example 49

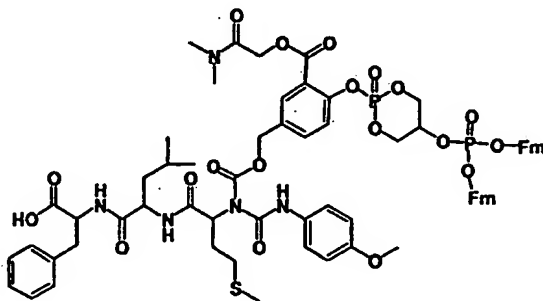
Compound 49 is similar to compound 47 except the masked phosphoantigen activators of γ/δ T cells have been replaced with ligands that will bind to the N-formyl peptide receptor after unmasking. Activation of the N-formyl peptide receptor will induce leukocyte chemotaxis, superoxide generation, and the release of inflammatory cytokines. These will all synergize with the immune response directed towards the neoantigens generated from the covalent modification of cathepsin B and the targeted trypsin like serine proteases. The N-formyl peptide receptor ligands are masked by esterase triggered clock like time delay tiggers. The following references relate to this subject matter:

Higgins J.D., et al., "N-Terminus Urea-Substituted Chemotactic Peptides: New Potent Agonists and Antagonists toward the Neutrophil fMLF Receptor," *J Med Chem*, 39(5):1013-1015 (1996), the contents of which are incorporated herein by reference in their entirety.



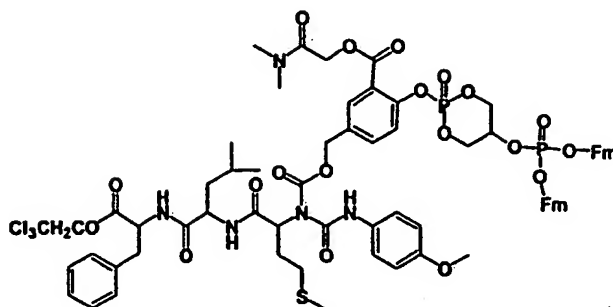
Compound 49 may be prepared by the methods described for compound 47 by

5 replacing compound 37.1 with compound 49.1.



Compound 49.1

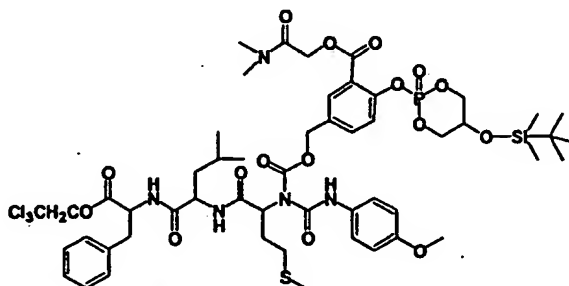
Compound 49.1 may be prepared by deprotection of compound 49.2 with Zn and acid.



Compound 49.2

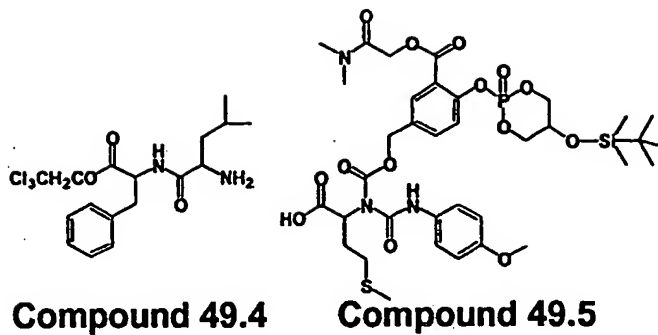
- 5 Compound 49.2 may be prepared by a multi-step process. Treating compound 49.3 with acid will remove the t-butyldimethylsilyl protecting group. Treating the product with phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester and a base such as triethylamine in an inert solvent will give compound 49.2.

- 10 Compound 49.3 may be prepared by coupling compounds 49.4 and 49.5.

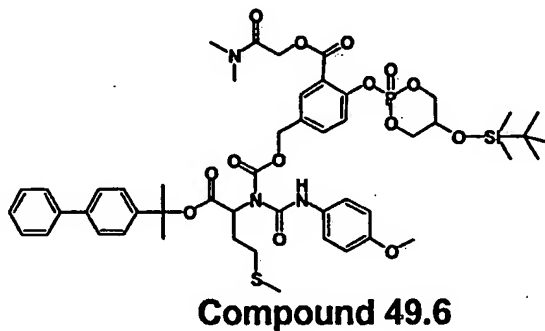


Compound 49.3

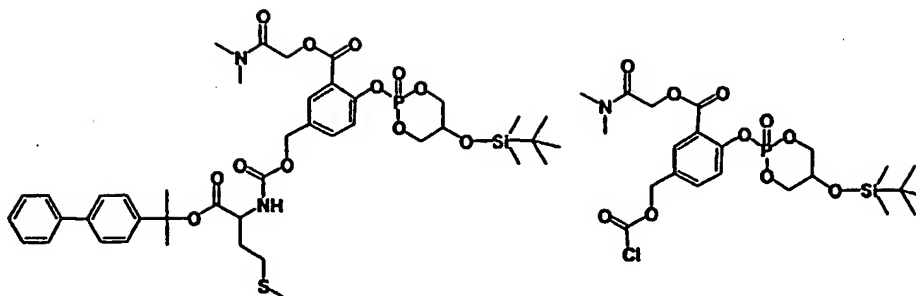
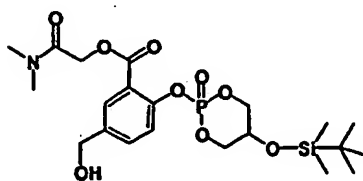
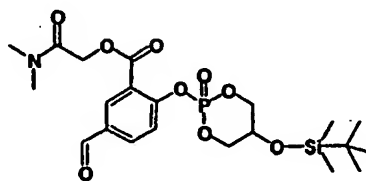
- Compound 49.4 may be synthesized from the L-amino acids using routine methods of peptide synthesis. Compound 49.5 may be prepared by treating compound 49.6 with dilute acid to cleave the 1-methyl-1-(4-biphenyl)ethyl ester group.
- 15



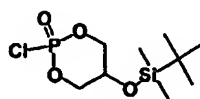
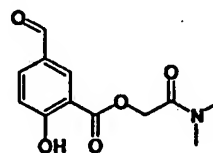
Compound 49.6 may be prepared by treating compound 49.7 with a strong base
 in an inert solvent at a low temperature such as -78°C and then reacting with
 5 phosgene and p-methoxyaniline.



Compound 49.7 may be prepared by reacting L-methionine 1-methyl-1-(4-
 biphenyl)ethyl ester with compound 49.8 in an inert solvent in the presence of
 base. Compound 49.8 may be prepared by treating compound 49.9 with
 10 phosgene and base in an inert solvent.

**Compound 49.7****Compound 49.8****Compound 49.9****Compound 49.9b**

- 5 Compound 49.9 may be prepared by reacting compound 33.2 with compound 49.10 in an inert solvent in the presence of base and then reducing the aldehyde (compound 49.9.b) by catalytic hydrogenation with palladium on carbon or by a reagent such as sodium borohydride.

**Compound 49.10****Compound 33.2**

10

Compound 49.10 may be prepared by reacting phosphorous oxychloride and 2-(tert-Butyl-dimethyl-silanyloxy)-propane-1,3-diol in an inert solvent in the presence of base.

Treating 2-Phenyl-[1,3]dioxan-5-ol with t-butyldimethylchlorosilane and base in an inert solvent and then hydrogenating with palladium on carbon will give -(tert-Butyl-dimethyl-silanyloxy)-propane-1,3-diol.

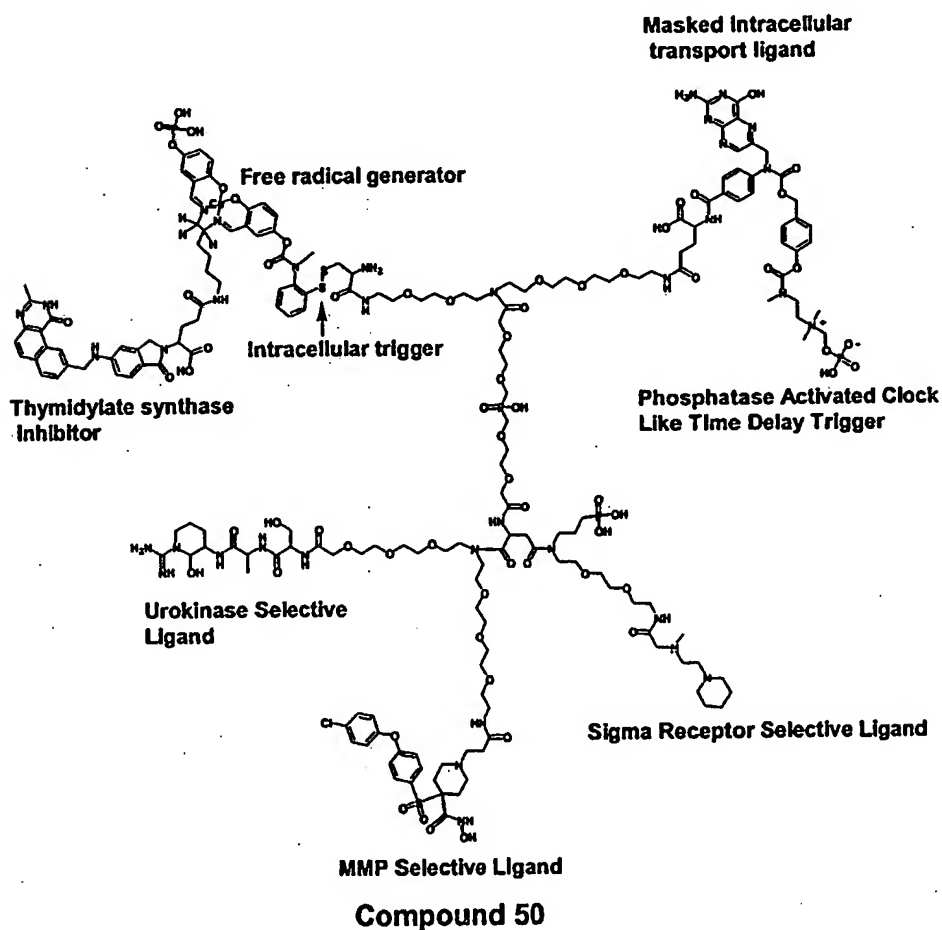
- 5 The neoantigens for sensitization purposes are the same as described for compound 47.

Example 50

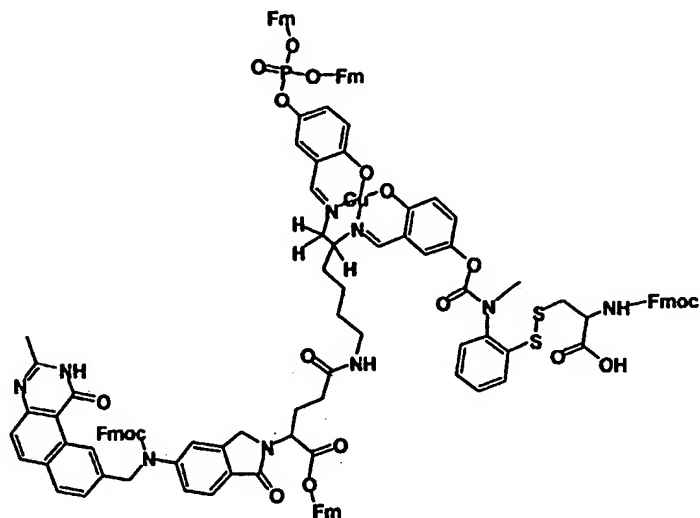
- 10 Compound 50 is similar to compound 43, however it has a potent inhibitor of thymidylate synthase 1843U89 to which is attached, by a short linker, a masked hydroxy-salen copper complex. Cleavage of the salen phosphate ester by phosphatase and of the intracellular trigger by thioreductases will free the hydroxy-salen copper- TS inhibitor complex from the remainder of the targeted
- 15 drug. The complex will bind tightly to TS. Free radicals generated by the copper complex will react with TS and induce neoantigens that may be used for targeted immunotherapy. Salen copper and salen iron complexes are known to generate free radicals under a variety of conditions. The presence of para hydroxy substituents on the salicylidene moieties leads to a radical generating system
- 20 from oxygen. The hydroxy substituted salicylidene moieties form hydroquinones, which cooperate in the redox reaction and aid in the generation of free radicals. Intracellularly a variety of mechanisms exist that can lead to redox cycling and the continued generation of free radicals. The following references relate to this subject matter: Lamour E., et al., "Oxidation of Cu^{II} to Cu^{III}", Free Radical
- 25 Production, and DNA Cleavage by Hydroxy-Salen-Copper Complexes. Isomeric Effects Studied by ESR and Electrochemistry," *J Am Chem Soc*, 121:1862-1869

(1999); Routier S., et al., "DNA Cleavage by Hydroxy-Salicylidene-Ethylendiamine-Iron Complexes," *Nucleic Acids Res*, 27(21):4160-4166 (1999); Routier S., et al., "Synthesis of a Functionalized Salen-Copper Complex and Its Interaction with DNA," *J Org Chem*, 61:2326-2331 (1996), the contents of which

5 are incorporated herein by reference in their entirety.

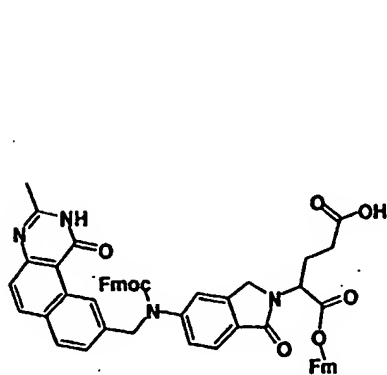


Compound 50 may be prepared by the methods described for compound 38 by replacing compound 21.2.1d with compound 18.1 and also replacing 38.1 with compound 50.1.

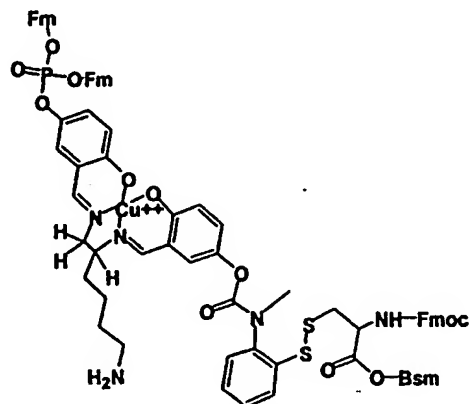


Compound 50.1

- 5 Compound 50.1 may be prepared by coupling compound 50.2 and compound 50.3 and then treating with tris(2-aminoethyl)amine to cleave the Bsm ester under conditions that will leave the Fmoc group intact. The synthesis of compound 50.2 is described in example 8 (compound 8.2.1).

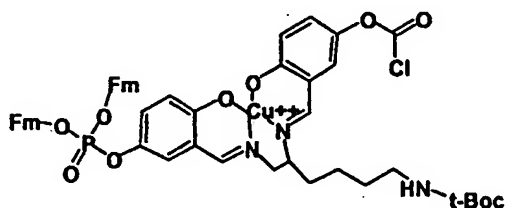
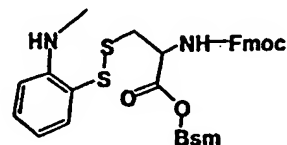
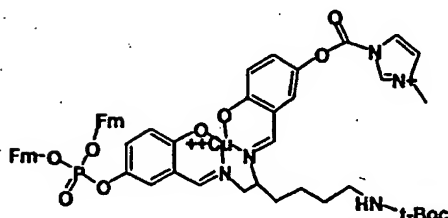
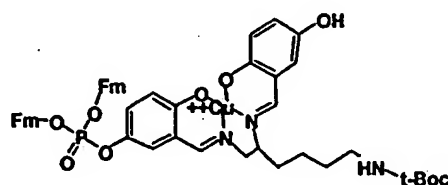


Compound 50.2



Compound 50.3

Compound 50.3 may be prepared by reacting compound 50.4 (or compound 50.4.1) and compound 50.5 in an inert solvent in the presence of base and then removing the t-Boc group with acid.

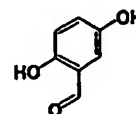
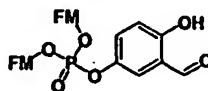
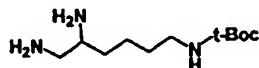
**Compound 50.4****Compound 50.5****Compound 50.4.1****Compound 50.4a**

5

Compound 50.4 may be prepared by treating compound 50.4a with phosgene in an inert solvent.

- 10 Compound 50.4.1 may be prepared by treating compound 50.4a with 1,1'-carbonylbis(3-methylimidazolium) triflate in an inert solvent at low temperature in the presence of base. The following references relate to this subject matter:
- Saha A.K., et al., "1,1'-Carbonylbis(3-methylimidazolium) Triflate: An Efficient Reagent for Aminoacylations," *J Am Chem Soc*, 111:4856-4859 (1989), the
- 15 contents of which are incorporated herein by reference in their entirety.

Compound 50.4a may be prepared by reacting compound 50.4b, compound 50.4c, compound 50.4d, and copper (II) acetate and isolating the desired product by chromatography.



Compound 50.4b Compound 50.4c Compound 50.4d

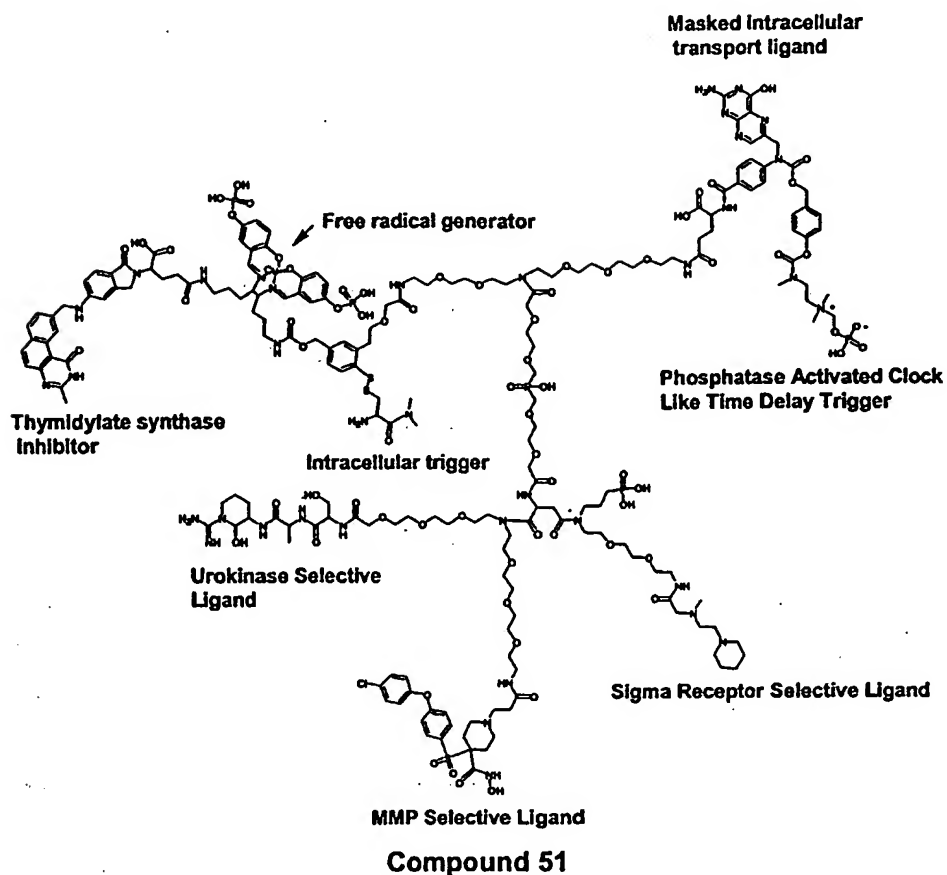
- 5 The following references relate to this subject matter: Lamour E., et al., "Oxidation of Cu^{II} to Cu^{III}, Free Radical Production, and DNA Cleavage by Hydroxy-Salen-Copper Complexes. Isomeric Effects Studied by ESR and Electrochemistry," *J Am Chem Soc*, 121:1862-1869 (1999); Routier S., et al., "Synthesis of a Functionalized Salen-Copper Complex and Its Interaction with
- 10 DNA," *J Org Chem*, 61:2326-2331 (1996), the contents of which are incorporated herein by reference in their entirety.

- Compound 50.4c may be prepared by treating 2-(tert-Butyl-dimethyl-silanyloxy)-5-hydroxy-benzaldehyde with phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester and a base such as triethylamine in an inert solvent and then
- 15 removing the silyl protecting group with acid.

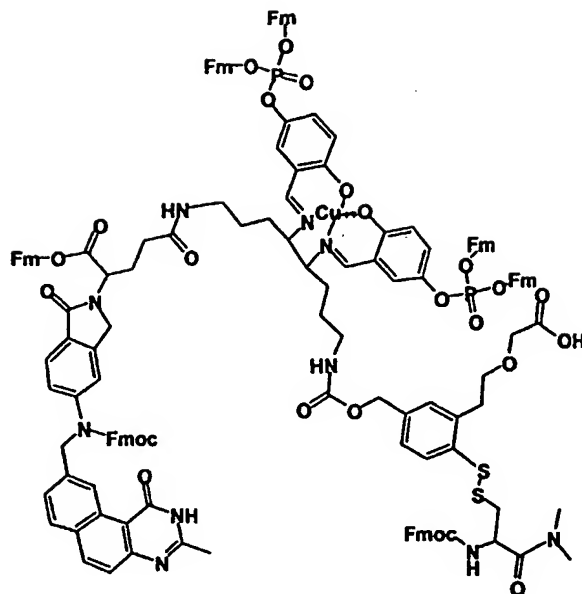
Example 51

- 20 Compound 51 is similar to compound 50, however the hydrox-salen copper complex is masked as phosphate esters, which will be cleaved by phosphatases to activate the free radical generator. The TS inhibitor –salen –copper complex

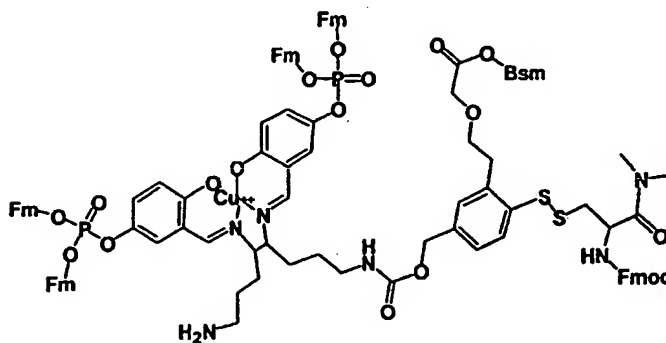
will be freed from the remainder of the drug by an intracellular trigger following activation by intracellular thioreductases.



- 5 Compound 51 may be prepared by the method described for compound 50 by replacing compound 50.1 with compound 51.1.

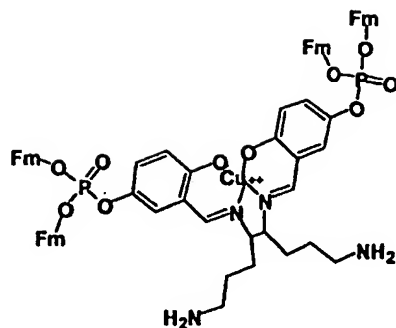
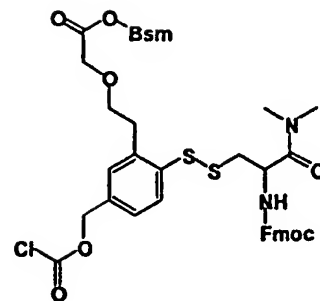
**Compound 51.1**

Compound 51.1 may be prepared by coupling compound 50.2 and compound 51.2 and then treating with tris(2-aminoethyl)amine to cleave the Bsm ester under conditions that will leave the Fmoc group intact.

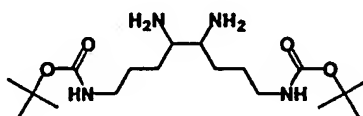
**Compound 51.2**

5

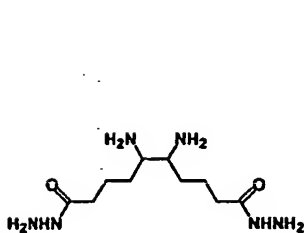
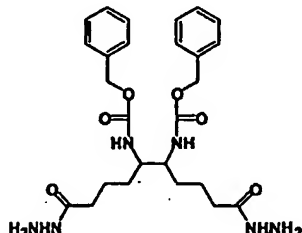
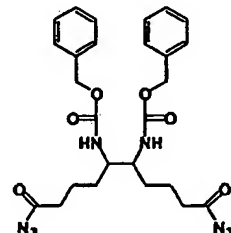
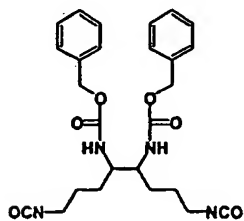
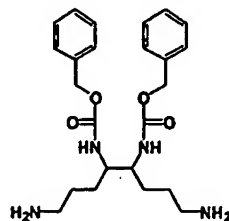
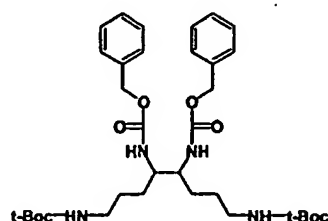
Compound 51.2 may be prepared by reacting compound 51.3 and compound 51.4 in an inert solvent in the presence of base.

**Compound 51.3****Compound 51.4**

Compound 51.3 may be prepared by reacting 2 equivalents of compound 50.4c, compound 51.5 and copper (II) acetate and then treating with acid to remove the t-Boc groups.

**Compound 51.5**

5

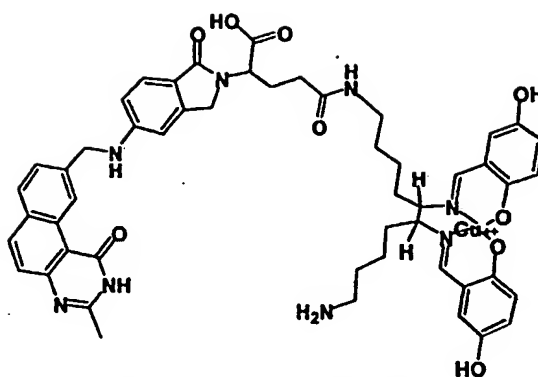
**Compound 51.5a****Compound 51.5b****Compound 51.5c****Compound 51.5d****Compound 51.5e****Compound 51.5f**

Compound 51.5 may be prepared by a multi-step process. Catalytic hydrogenation of [2,2']Bipyridinyl-6,6'-diol with Pd on carbon will give [2,2']Bipiperidinyl-6,6'-dione. Treatment with hydrazine will give compound

- 5 51.5a. Reaction with 2 equivalents of benzyl chloroformate and base will protect the more reactive amino groups and give compound 51.5b. Treatment with sodium nitrite and acid will give compound 51.5c. Heating will, via the Curtius rearrangement, give compound 51.5d. Hydrolysis will give compound 51.5e. Treatment with di-t-butyl pyrocarbonate and in an inert solvent will give
- 10 compound 51.5f. Catalytic hydrogenation will give compound 51.5.

Compound 51.4 may be prepared by the methods described for the synthesis of compound 23.2b by replacing compound 14.11.4 with L-N-Fmoc-cysteine N,N-dimethylamide.

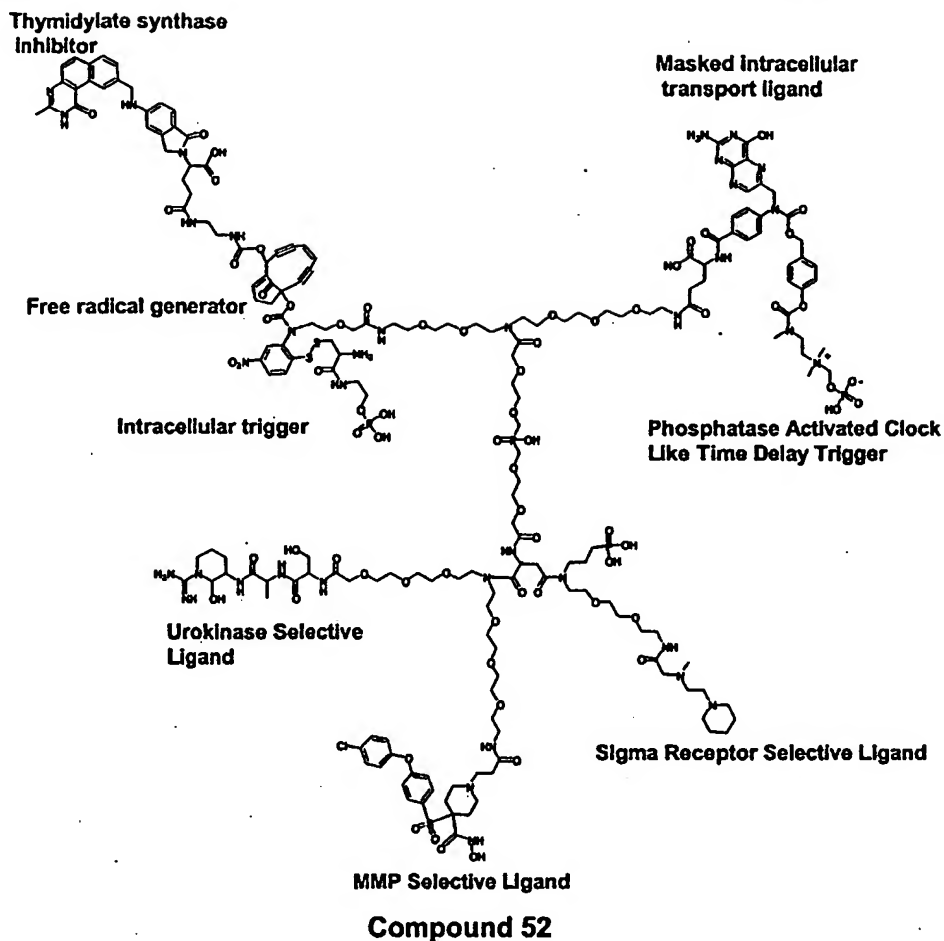
- 15 The neoantigens, for sensitization purposes, may be prepared by treating thymidylate synthase with a compound such as compound 51.6 in the presence of oxygen and a reducing agent such as ascorbic acid so that a redox cycle can be established leading to augmented hydroxy radical production. Alternatively, the compounds derived from the interaction of TS and compound 51.6 may be
- 20 identified, synthesized and employed.



Compound 51.6

Example 52

- 5 Compound 52 is similar to compound 51, however, an enediyne analog is employed to generate free radicals and create neoantigens from the enzyme TS. The following references relate to this subject matter: Zein N., et al., "Protein Damage Caused by a Synthetic Enediyne Core," *Biorg Med Chem Lett*, 3(6):1351-1356 (1993); Kadow J.F., et al., "Conjugate Addition-Aldol Approach to
- 10 the Simple Bicyclic-Diynene Core Structure Found in the Esperamicins and Calicheamicins," *Tetrahedron Lett*, 33(11):1423-1426 (1992); 5,395,849 3/7/95 Wittman, et al., "Hybrid Antitumor Compounds Containing a Cyclic Enediyne and a DNA-Binder"; 5,198,560 3/30/93 Kadow, et al., "Cytotoxic Bicyclo[7.3.1]Tridec-4-Ene-2,6-Diyne Compounds and Process for the
- 15 Preparation Thereof", the contents of which are incorporated herein by reference in their entirety.

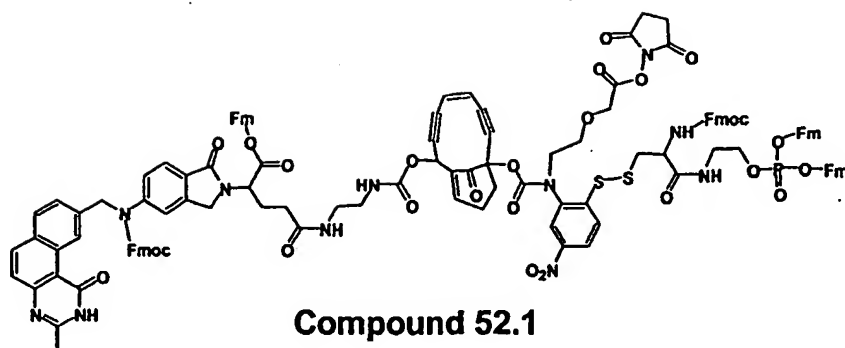


Compound 52 may be prepared by the method described for compound 50 by

5 replacing compound 50.1 with compound 52.1. Also, the order of deprotection of compound 21.1.1 should be modified, as Bsm deprotection with tris(2-aminoethyl)amine may not be compatible with preservation of the enediyne.

Compound 21.1.1 should have the Bsm group removed prior to reacting with compound 52.1. This leaves a free carboxylate group and requires that

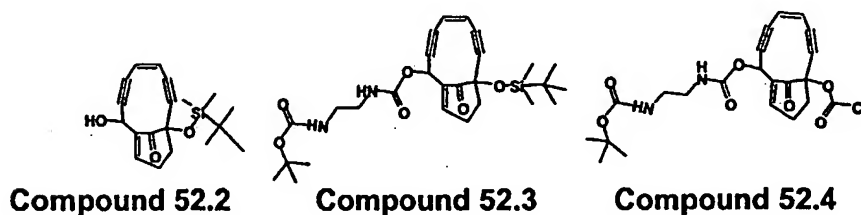
10 compound 31.1 to be converted into an active ester such as an N-hydroxysuccinimide ester for its coupling reaction to avoid unwanted side products.



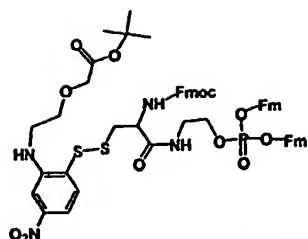
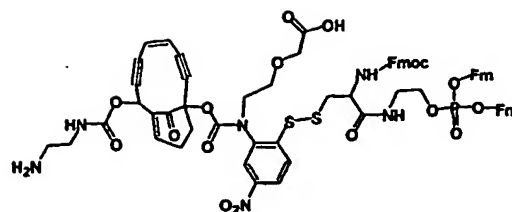
Compound 52.1 may be prepared in a multi-step process. Compound 52.2 may be treated with phosgene in an inert solvent at low temperature and then reacted

5 with (2-Amino-ethyl)-carbamic acid tert-butyl ester to give compound 52.3.

Selective removal of the t-butyldimethylsilyl protecting group with acid followed by treatment with phosgene in an inert solvent will give compound 52.4.

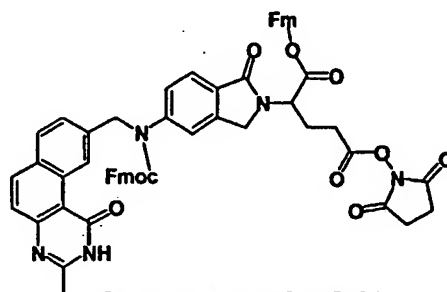


10 Compound 52.4 may be reacted with compound 52.5 in an inert solvent in the presence of base. Treatment of the product with acid will cleave the t-Boc and t-butyl ester groups and give compound 52.6.

**Compound 52.5****Compound 52.6**

Compound 52.6 may then be reacted with compound 52.7. Treatment of the product with a reagent such as dicyclohexylcarbodiimide and N-hydroxysuccinimide will give compound 52.1.

5

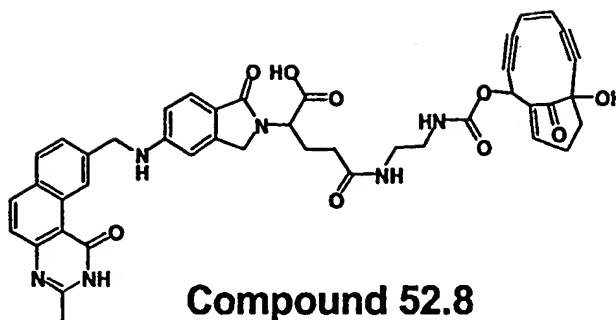
**Compound 52.7**

Compound 52.7 may be prepared by coupling of compound 50.2 with N-hydroxysuccinimide using a reagent such as dicyclohexylcarbodiimide.

10

The neoantigens, for sensitization purposes, may be prepared by treating TS with a compound, such as compound 52.8 in the presence of a thiol, such as cysteine to initiate diradical formation. Alternatively, the synthetic oligopeptides that correspond to the family of TS derived products generated by the interaction of activated compound 52.8 and TS may be employed.

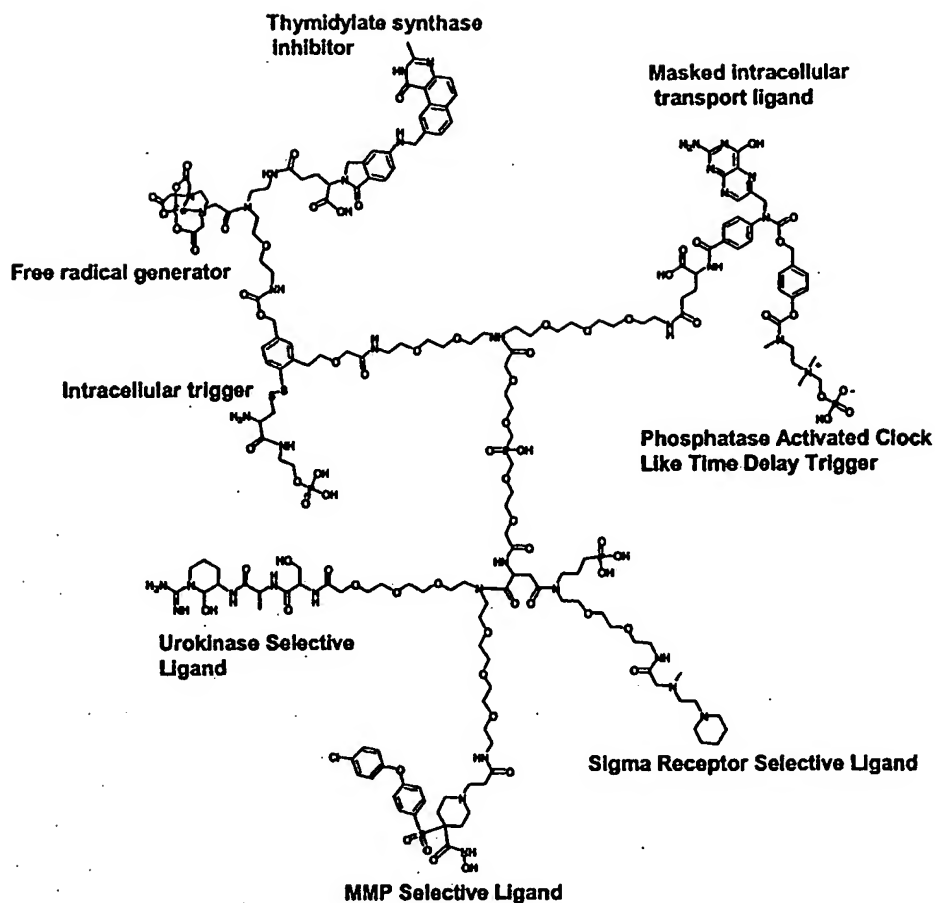
15



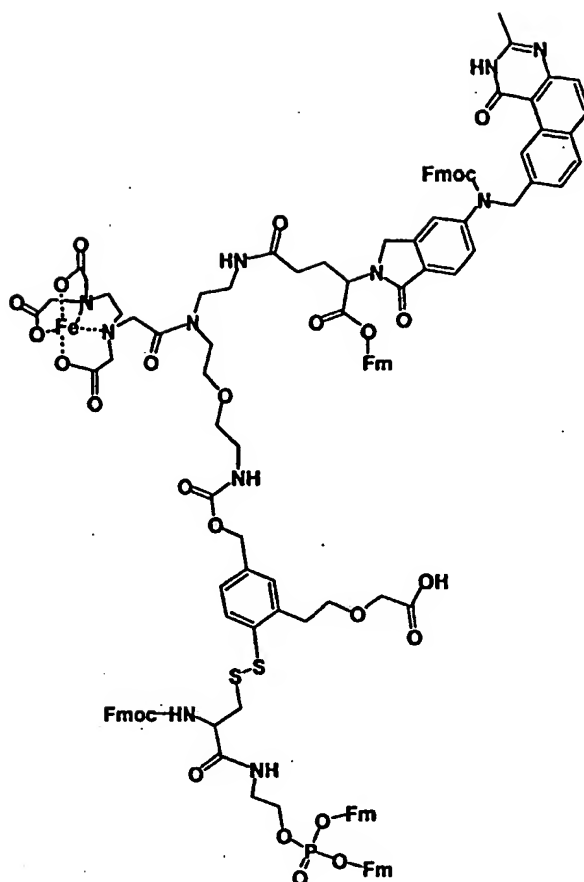
Example 53

Compound 53 is similar to compound 52, however in a chelate of Iron (II) is employed as a free radical generator to create neoantigens from TS. Iron (II) complexes with chelating agents are known to generate free radicals under a variety of conditions. The following references relate to this subject matter:

Kocha T., et al., "Hydrogen Peroxide-mediated Degradation of protein: Different Oxidation Modes of Copper- and Iron-dependent Hydroxyl Radicals on the Degradation of Albumin," *Biochem Biophys Acta*, 1337:319-326 (1997); Egan T.J., et al., "Catalysis of the Haber-Weiss Reaction by Iron-Diethylenetriaminepentaacetate," *J Inorg Biochem*, 48:241-249 (1992); Hertzberg R.P.; Dervan P.B., "Cleavage of DNA with Methidiumpropyl-EDTA-Iron (II): Reaction Conditions and Product Analyses," *Biochemistry*, 23:3934-3945 (1984); Schepartz A.; Cuenoud B., "Site-Specific Cleavage of the Protein Calmodulin Using a Trifluoperazine-Based Affinity Reagent," *J Am Chem Soc*, 112:3247-3249 (1990), the contents of which are incorporated herein by reference in their entirety.

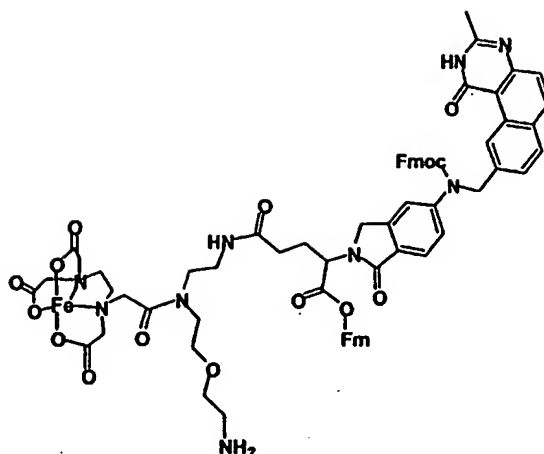
**Compound 53**

Compound 53 may be prepared as described for compound 50 by replacing compound 50.1 with compound 53.1.

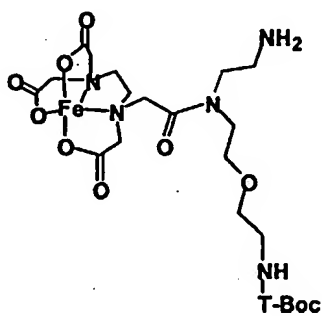


Compound 53.1

- Compound 53.1 may be prepared by reacting compound 53.2 and compound 23.2b in an inert solvent, in the presence of base, and then treating with tris(2-aminoethyl)amine to cleave the Bsm ester under conditions that will leave the
- 5 Fmoc groups intact.

**Compound 53.2**

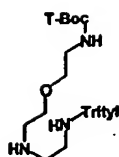
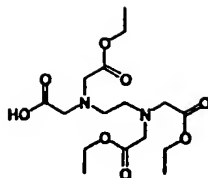
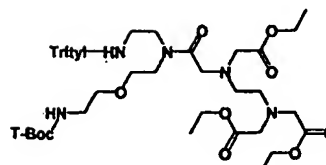
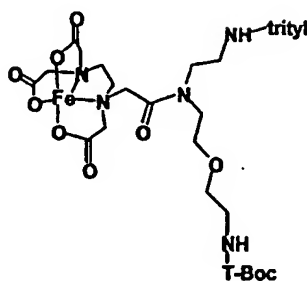
Compound 53.2 may be prepared by reacting compound 53.3 and compound 52.7 and then treating with acid to remove the t-Boc group.

**Compound 53.3**

5

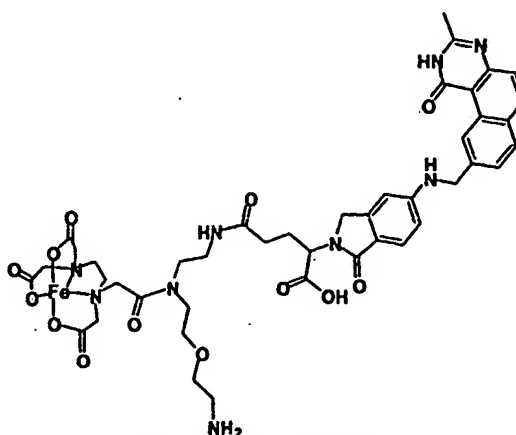
Compound 53.3 may be prepared by a multi-step procedure. Coupling compound 53.4 and compound 53.5 will give compound 53.6. Hydrolysis of the ethyl esters and treatment with an Iron (II) salt will give compound 53.7. The

10 trityl protecting group may then be selectively removed by treatment with acid to give compound 53.3.

**Compound 53.4****Compound 53.5****Compound 53.6****Compound 53.7**

Compound 53.4 may be prepared by reacting benzenesulfonic acid 2-(2-tert-butoxycarbonylamino-ethoxy)-ethyl ester and N1-Trityl-ethane-1,2-diamine in an

5 inert solvent in the presence of base.

**Compound 53.8**

Neoantigens, for sensitization purposes, may be prepared by treating TS with a compound such as compound 53.8 in the presence of hydrogen peroxide, or hydrogen peroxide and ascorbic acid, or with a thiol base reducing agent under

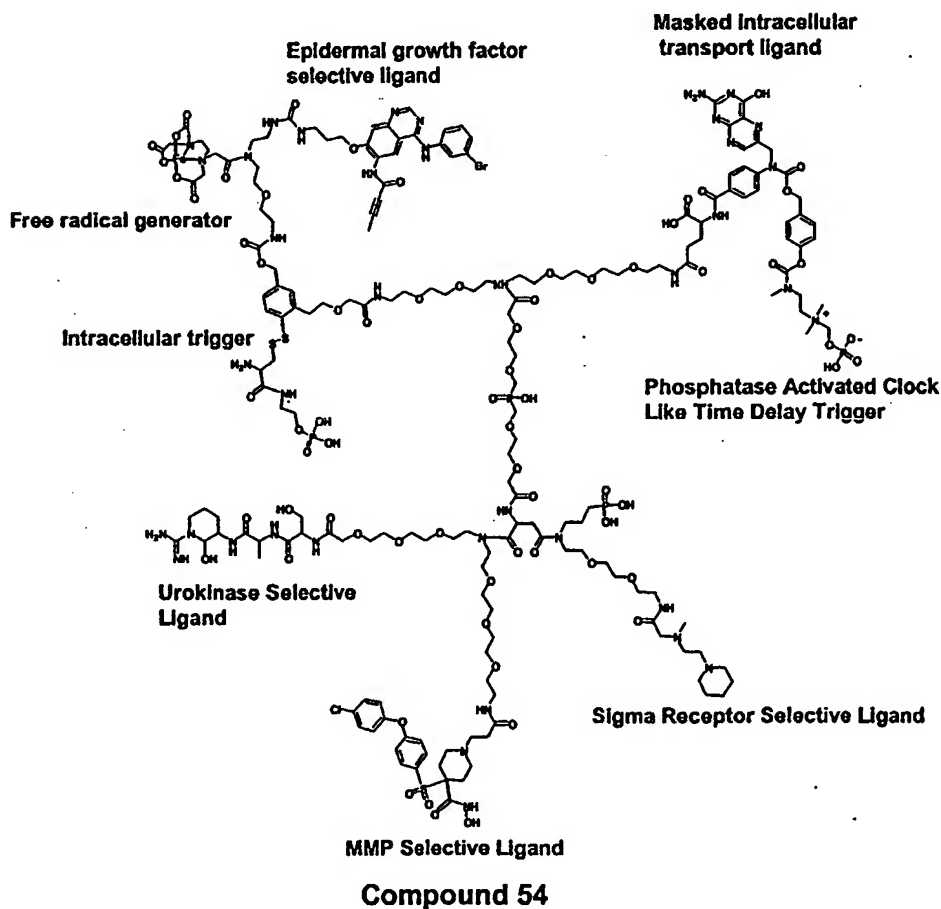
10 aerobic conditions. Alternatively, synthetic oligopeptides corresponding to the

degradation products, resulting from the interaction of compound 53.8 with TS under Fenton conditions may be employed.

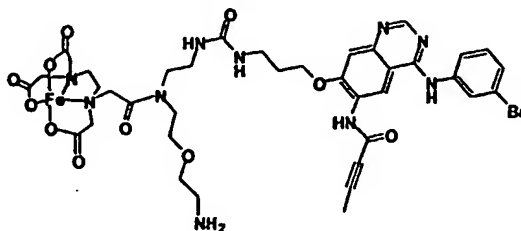
5 Example 54

Compound 54 is similar to compounds 34 and compound 53. Compound 54 will generate neoantigens from epidermal growth factor receptors by both covalent modification of the active site of the enzyme and by Fenton chemistry induced free radical damage to the enzyme.

10



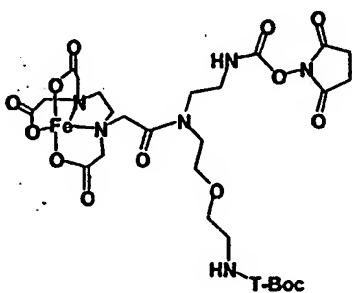
Compound 54 may be prepared by the method described for compound 53 by replacing compound 53.2 with compound 54.1.



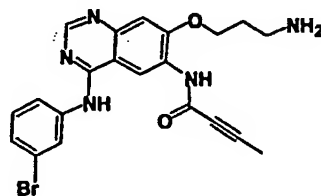
Compound 54.1

5

Compound 54.1 may be prepared by reacting compound 34.2 and compound 54.2 and then treating with acid to remove the t-Boc group.



Compound 54.2



Compound 34.2

10

Compound 54.2 may be prepared by treating compound 53.3 with N,N'-disuccinimidyl carbonate in an inert solvent in the presence of pyridine.

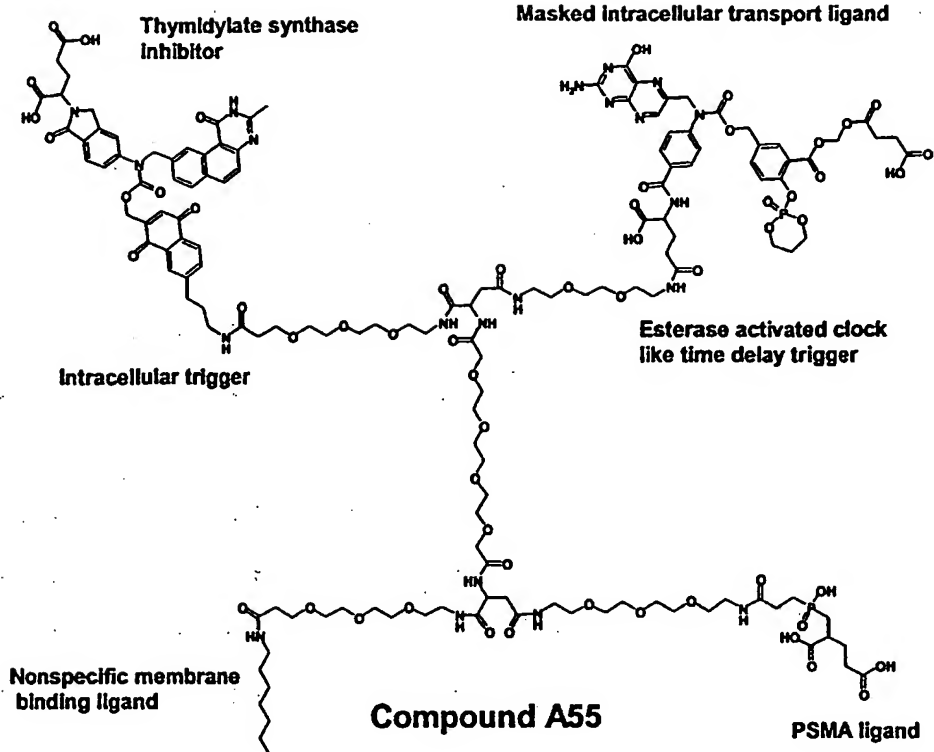
15 The neoantigens, for sensitization purposes, may be prepared by treating the respective epidermal growth factor related target with a compound such as

compound 54.1 under conditions as described in example 53. Alternatively, the corresponding synthetic oligopeptides may be employed.

5 Example 55

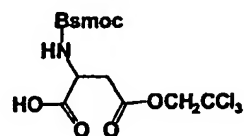
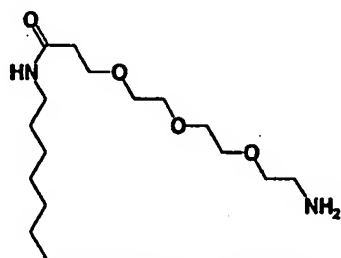
Compounds A55 and B55 are a set of monofactorial drugs that will exhibited target synergistic toxicity and multifactorial targeting when administered in combination. Compound A55 will deliver a thymidylate synthase inhibitor to prostate specific membrane antigen positive cells. Compound B55 will deliver a
10 nucleoside transport inhibitor to urokinase positive cells. Prostatic cancer cells that jointly express both urokinase and PSMA will have both denovo and salvage pathways of thymidine metabolism inhibited and will be selectively killed.

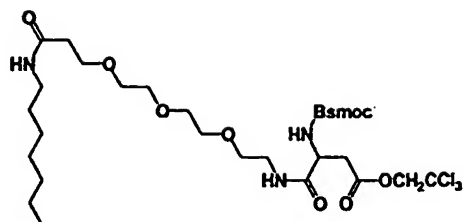
Compound A55 has a PSMA targeting ligand, a fatty amide ligand that will bind
15 nonspecifically, but weakly to cell membranes and a masked intracellular transport ligand with an esterase activated time delay clock like trigger. A potent inhibitor of TS (1843U89) will be released upon activation of an intracellular trigger. The intracellular trigger may be activated either by reduction of the quinone, by DT-diaphorase, or by nucleophilic activation by glutathione. The
20 following references relate to this subject matter: Flader C., et al., "Development of Novel Quinone Phosphorodiamidate Prodrugs Targeted to DT-Diaphorase," *J Med Chem*, 43:3157-3167 (2000), the contents of which are incorporated herein by reference in their entirety.



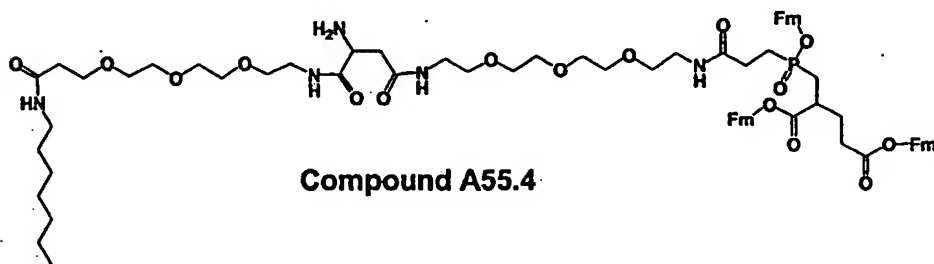
Compound A55 may be prepared by a multi-step process. Compounds A55.1 and A55.2 may be coupled to give compound A55.3.

5

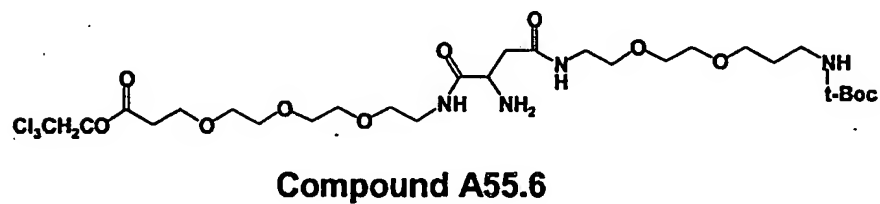
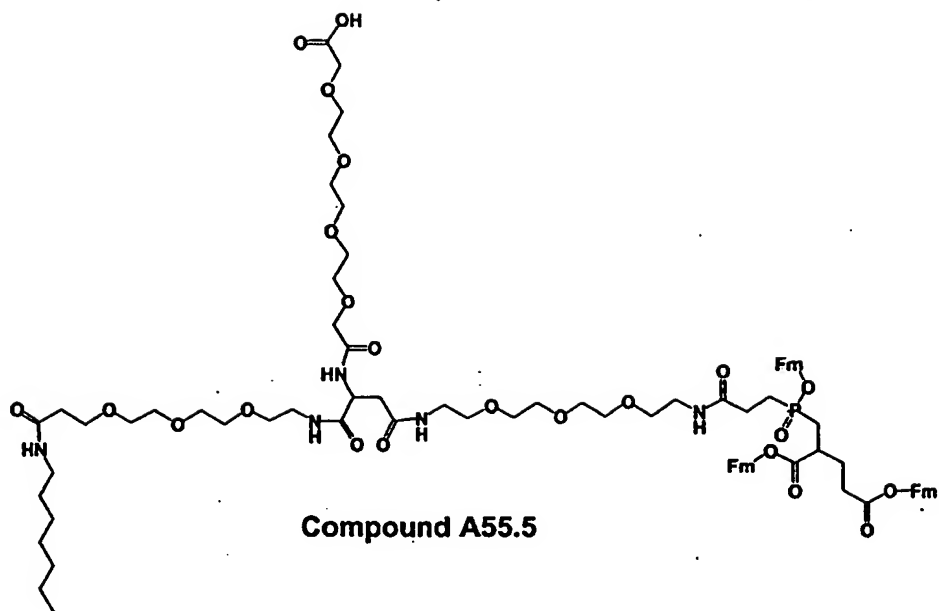


**Compound A55.3**

Treatment with Zn and acid, followed by coupling to compound 44.3, followed by
removal of the Bsmoc protecting group with tris(2-aminoethyl)amine under
5 conditions that will leave the Fmoc group intact, will give compound A55.4.

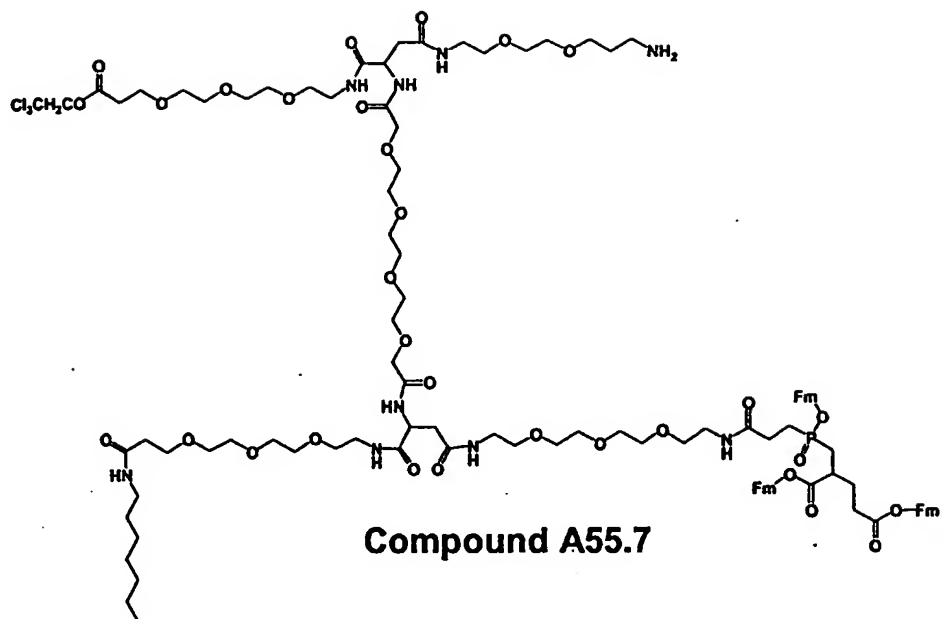
**Compound A55.4**

Coupling compound A55.4 and (2-{2-[2-(2,2,2-Trichloro-
10 ethoxycarbonylmethoxy)-ethoxy]-ethoxy}-ethoxy)-acetic acid followed by
treatment with Zn and acetic acid will give compound A55.5.

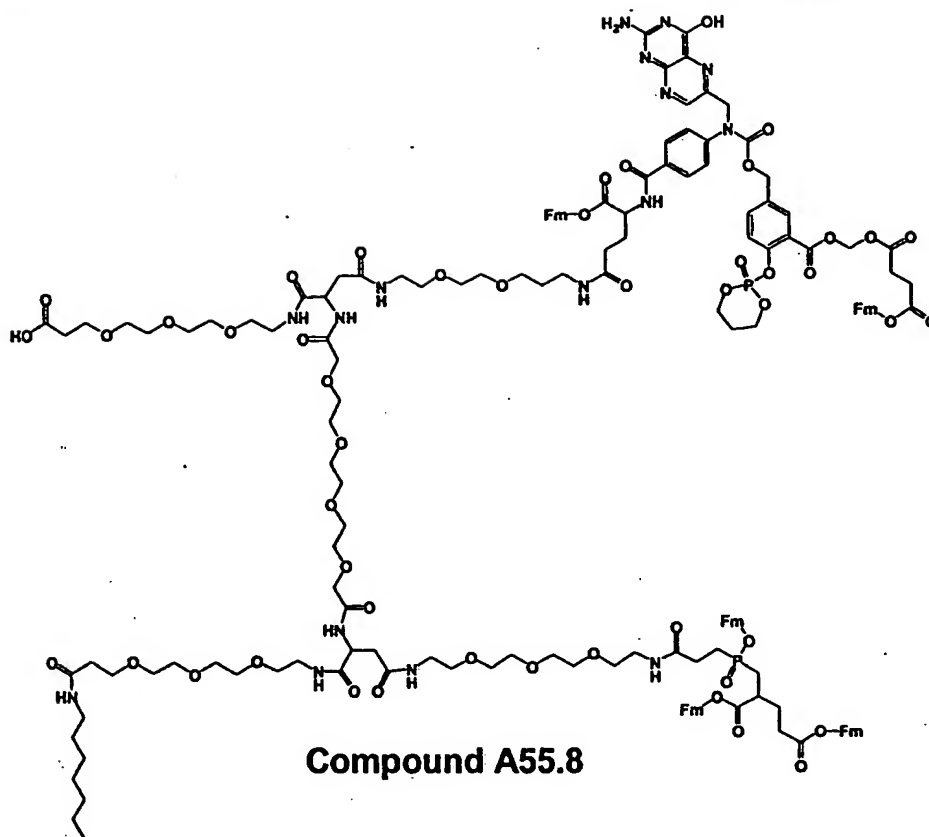


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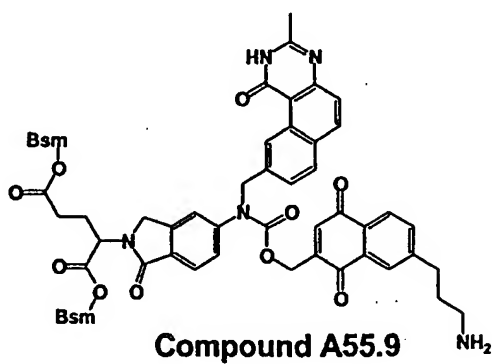
Coupling compound A55.5 and compound A55.6 and treating with acid to remove the T-boc group will give compound A55.7.



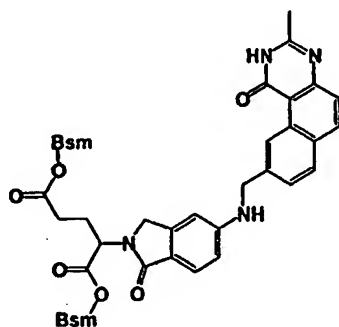
- Coupling compound A55.7 and compound 32.1, followed by the removal of the
- 5 trichloroethyl protecting group with Zn and acetic acid, will give compound A55.8.



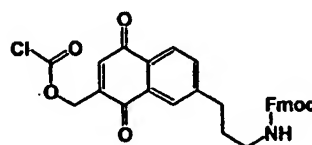
Coupling compound A55.8 with compound A55.9 followed by treatment with
 5 base to remove the Fmoc and Fm groups will give compound A55.



Compound A55.9 may be prepared by reacting compound A55.10 and A55.11 in an inert solvent in the presence of a base such as pyridine and then treating with a base such as diisopropylethylamine to selectively remove the Fmoc group without cleaving the Bsm esters.



Compound A55.10



Compound A55.11

5

Compound A55.10 may be prepared by a multi-step process. The TS inhibitor 1843U89 may be treated with an excess of a reagent such as hexamethyldisilazane and a catalytic amount of chlorotrimethylsilane in an inert solvent. The following references relate to this subject matter: Duch D.S., et al., "Biochemical and Cellular Pharmacology of 1843U89, a Novel Benzoquinazoline Inhibitor of Thymidylate Synthase," *Cancer Res*, 53:810-818 (1993); Pendergast W., et al., "Benzo[*f*]quinazoline Inhibitors of Thymidylate Synthase: Methyleneamino-Linked Arylglutamate Derivatives," *J Med Chem*, 37:838-844 (1994), the contents of which are incorporated herein by reference in their entirety.

15

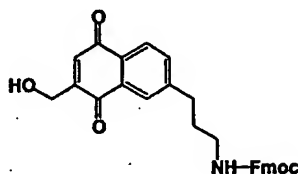
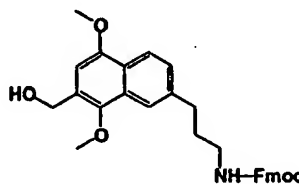
The product may then be reacted with benzyl chloroformate, followed by oxalyl chloride and catalytic amount of dimethylformamide. The resulting acid chloride may then be reacted with (1,1-Dioxo-1H-1λ6-benzo[*b*]thiophen-2-yl)-methanol

20

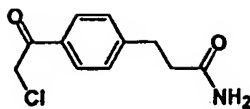
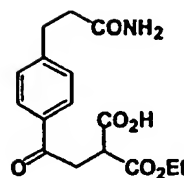
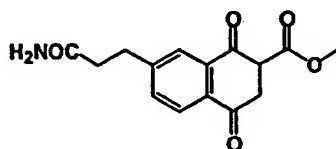
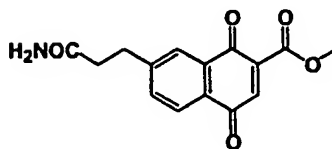
and base. Catalytic hydrogenation, with palladium on carbon, will remove the benzyloxycarbonyl protecting group and give compound A55.10.

In an alternate method, compound A55.9 may be prepared by reacting compound A55.11b and compound A55.10 in an inert solvent in the presence of
5 a base such as pyridine and oxidizing of the product with a reagent such as cerium ammonium nitrate, and then removing the Fmoc group with diisopropylethylamine.

Compounds A55.11 and A55.11b may be prepared by reacting compounds
10 A55.12 and A55.12b respectively with phosgene in an inert solvent.

**Compound A55.12****Compound A55.12b**

Compound A55.12 may be prepared by a mult-step process. The compound 4-
15 (2-chloroethyl)acetophenone may be converted into 2-[4-(2-Chloro-ethyl)-phenyl]-2-methyl-[1,3]dioxolane by treatment with acid and ethylene glycol. Treatment with sodium cyanide will give 3-[4-(2-Methyl-[1,3]dioxolan-2-yl)-phenyl]-propionitrile. Acid hydrolysis will give 3-(4-Acetyl-phenyl)-propionamide. Treatment with copper (II) chloride will give compound A55.13.

**Compound A55.13****Compound A55.14****Compound A55.15****Compound A55.16**

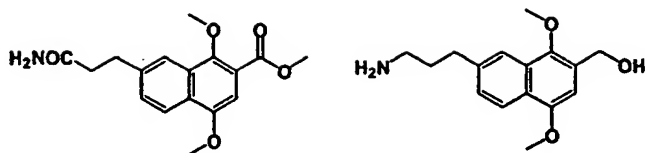
Treatment of A55.15 with diethylmalonate and a strong base in an inert solvent, followed by hydrolysis of one of ethyl ester groups with base, will give compound

- 5 A55.14. Treatment of compound A55.14 with anhydrous HF will give compound A55.15. The following references relate to this subject matter: Fieser L.F.; Hershberg E.B. "Inter- and Intramolecular Acylations with Hydrogen Fluoride," *J Am Chem Soc*, 61:1272-1281 (1939), the contents of which are incorporated herein by reference in their entirety.

10

A55.15 may be halogenated with an agent such as bromine or copper (II) chloride and then the product should be treated with base to give the elimination product A55.16. Catalytic hydrogenation with Pd on carbon, followed by treatment with methyl iodide and base, will give compound A55.17. Reduction

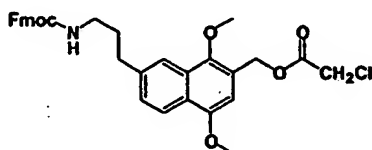
15 with lithium aluminum hydride in an inert solvent will give compound A55.18. Treatment with 9-fluorenylmethyl chloroformate in an inert solvent will give compound A55.12.b.



Compound A55.17 Compound A55.18

Treatment of compound A55.12b chloro-acetic anhydride and base will give compound A55.19.

5



Compound A55.19

Oxidation with cerium (IV) ammonium nitrate in an inert solvent followed by hydrolysis of the chloroacetate ester will give compound A55.12.

10

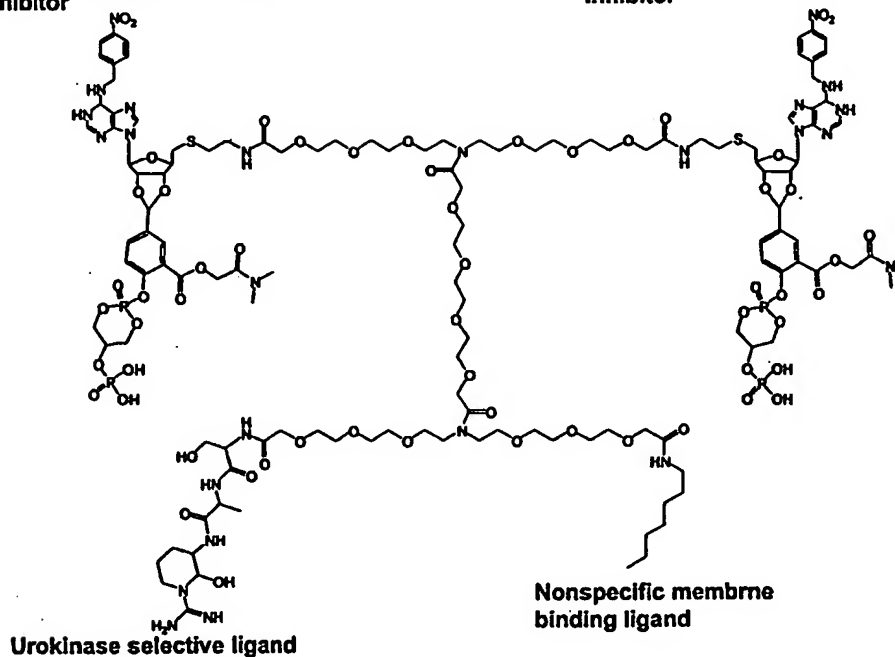
Compound B55 has a targeting ligand for urokinase, a low affinity nonspecific membrane binding ligand, and two masked "5'-S-(2-Aminoethyl)-N6-(4-Nitrobenzyl)-5'-Thioadenosine ligands, which when unmasked, will bind tightly to nucleoside transport inhibitors on the surface of targeted cells. The nucleoside

15 transport inhibitors are masked by an esterase activated time delay clock like trigger. Its expected rate-limiting step will be the intramolecular nucleophilic attack of the carboxylate group on the phosphotriester, which should proceed with a half life of approximately 90 minutes. The unmasked phenolic hydroxy group, which is in equilibrium with the powerfully electron donating oxyanion, will

trigger rapid acetal cleavage by stabilizing carbocation formation at the benzylic carbon.

Masked Nucleoside transport inhibitor

Masked Nucleoside transport inhibitor

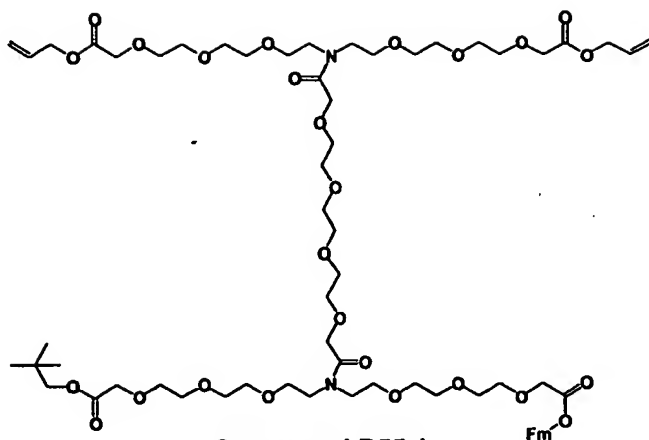


Compound B55

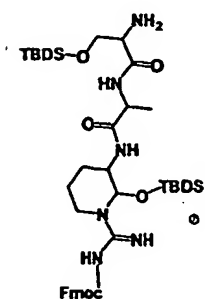
5

Compound B55 may be prepared by a multi-step process. Treating compound B55.1 with base to cleave the Fm ester, followed by coupling to heptylamine, followed by acid treatment to cleave the t-butyl ester, followed by coupling to compound B55.2 will give compound B55.3. Cleavage of the allyl esters with Pd (0) and coupling to compound B55.4 will give B55.5. Treatment with base will remove the Fmoc and Fm protecting groups. The t-butyldimethylsilyl protecting groups may then be removed with a reagent such as t-butylammonium fluoride or by treatment with acid under conditions that do not cleave the acetal groups to give compound B55.

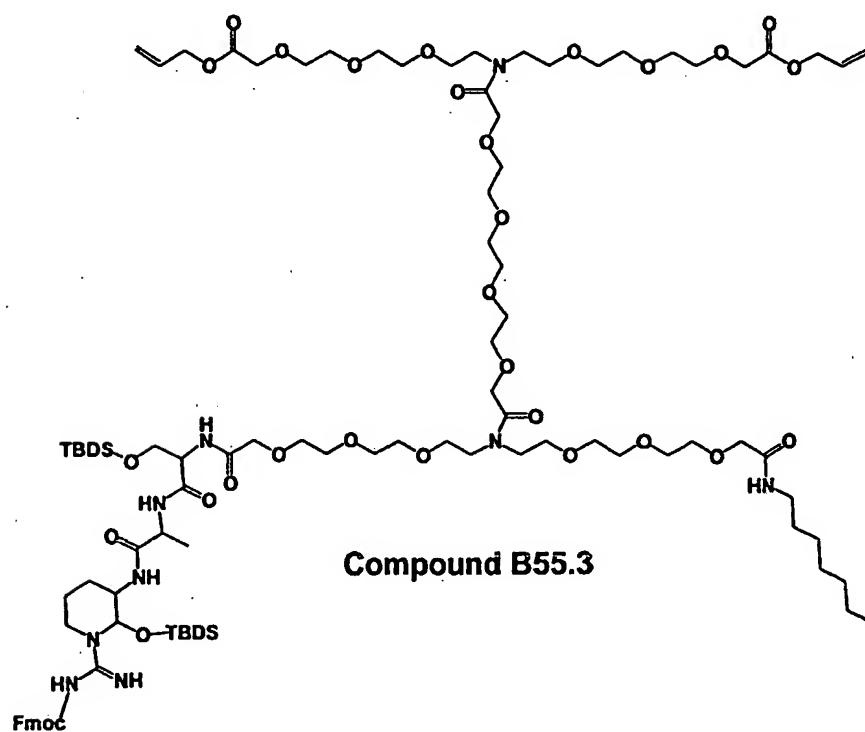
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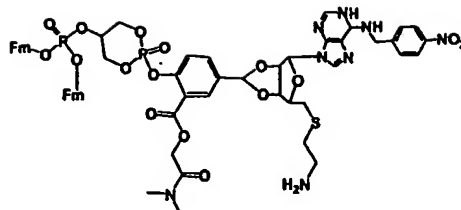
Compound B55.1



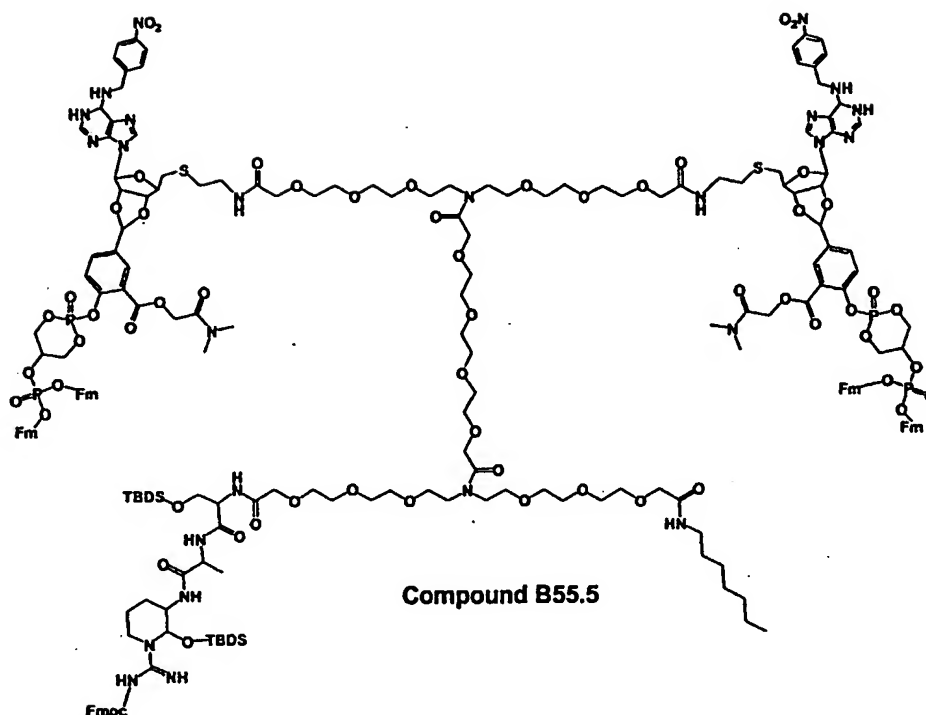
Compound B55.2



Compound B55.3



Compound B55.4

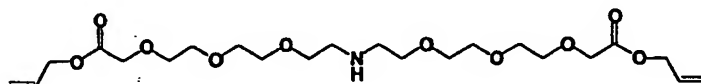
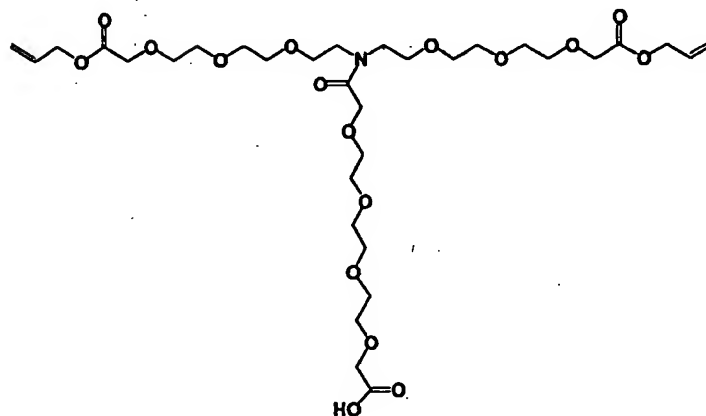


Compound B55.5

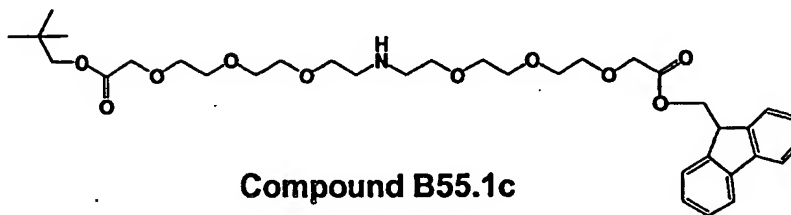
- Compound B55.1 may be prepared by a multi-step process. Treating {2-[2-(2-{2-[2-(2-Carboxymethoxy-ethoxy)-ethoxy]-ethylamino)-ethoxy]-ethoxy}-ethoxy)-acetic acid (compound B55.1d) with di-t-butyl pyrocarbonate and in an inert solvent will give [2-(2-[2-[(2-[2-(2-Carboxymethoxy-ethoxy)-ethoxy]-ethyl)-(3,3-dimethyl-butyryl)-amino]-ethoxy)-ethoxy)-ethoxy]-acetic acid. Esterification with allyl alcohol followed by acid treatment to remove the t-Boc group will give {2-[2-
- 5 [2-(2-[2-(2-Allyloxycarbonyl-methoxy-ethoxy)-ethoxy]-ethylamino)-ethoxy]-
- 10 (2-[2-[2-(2-Allyloxycarbonyl-methoxy-ethoxy)-ethoxy]-ethylamino)-ethoxy)-

ethoxy]-ethoxy)-acetic acid allyl ester (compound B55.1a). This may be coupled to {2-[2-(2-tert-Butoxycarbonylmethoxy-ethoxy)-ethoxy]-ethoxy}-acetic acid and the product treated with acid to remove the t-butyl ester to give compound B55.1b.

5

**Compound B55.1a****Compound B55.1b**

Compound B55.1b may be coupled to compound B55.1c to give compound 55.1.

**Compound B55.1c**

10

Compound B55.1c may be prepared by a multi-step process. The compound {2-[2-(2-{2-[2-(2-Carboxymethoxy-ethoxy)-ethoxy]-ethylamino}-ethoxy)-ethoxy]-ethoxy}-acetic acid may be treated with 2,2,2 trichloroethyl chloroformate and base in an inert solvent or under Schotten-Bauman conditions. The product may then be esterified with one equivalent of t-butyl alcohol and [2-(2-[2-((2-[2-(2-(2,2-Dimethyl-propoxycarbonylmethoxy)-ethoxy)-ethoxy)-ethyl)-(2,2,2-trichloroethoxycarbonyl)-amino]-ethoxy)-ethoxy)-ethoxy]-acetic acid isolated. This may then be esterified with (9H-Fluoren-9-yl)-methanol and treated with Zn and acetic acid to give compound B55.1c.

10

Compound B55.1d may be prepared by reacting {2-[2-(2-Chloro-ethoxy)-ethoxy]-ethoxy}-acetic acid tert-butyl ester and {2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-acetic acid tert-butyl ester in an inert solvent in the presence of base, purifying the product by chromatography and then removing the t-butyl ester groups with acid.

15

Compound B55.4 may be prepared by a multi-step process. Compound 49.9b may be deprotected with tetrabutylammonium fluoride and treated with Phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester in an inert solvent, and the product treated with an excess of 2,2-dimethoxypropane and acid to give compound B55.4.1. This compound may be reacted with 5'-S-[2-(1,1-dioxobenzo[b]thiophen-2-yloxy-carbonylamino)ethyl]-N6-(4-nitrobenzyl)-5'-thioadenosine in presence of an acid, and the product can be selectively deprotected with tris(2-aminoethyl)amine to give compound B55.4.1. 5'-S-[2-(1,1-dioxobenzo[b]thiophen-2-yloxy-carbonylamino)ethyl]-N6-(4-nitrobenzyl)-5'-thioadenosine can be prepared by reacting of 5'-S-(2-aminoethyl)-N6-(4-

20

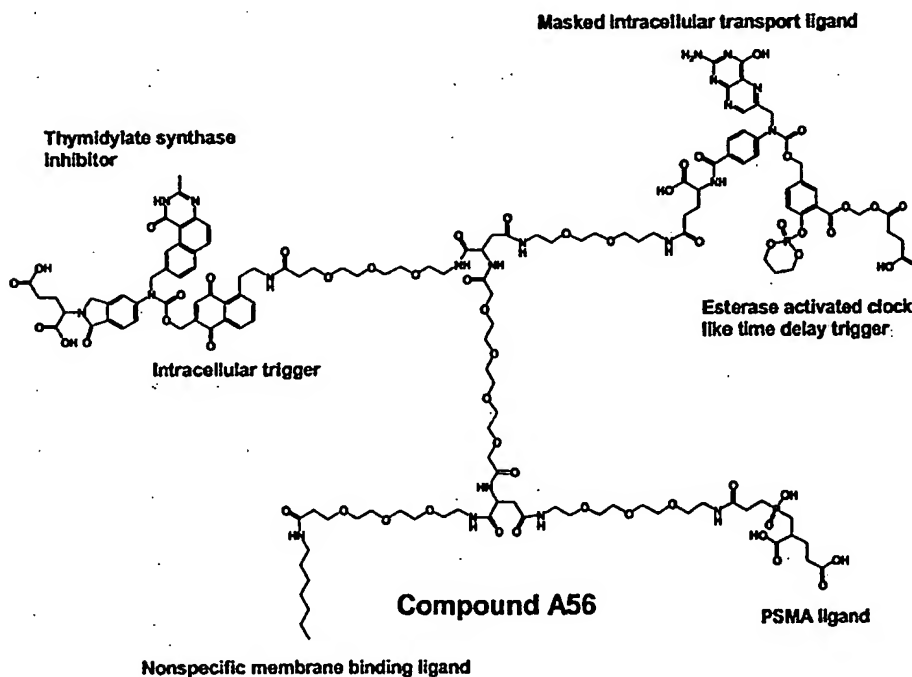
25

nitrobenzyl)-5'-thioadenosine with 1,1-dioxobenzo[b]thiophen-2-ylloxycarbonyl chloride. 5'-S-(2-aminoethyl)-N6-(4-nitrobenzyl)-5'-thioadenosine is a known compound.

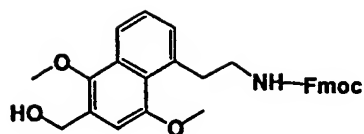
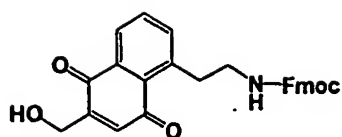
- 5 Compound B55.2 can be prepared by a method analogous to the method used for compound 14.7

Example 56

- Example 56 is similar to example 55. However, compound A55 is replaced with
10 compound A56 that has a different intracellular trigger.

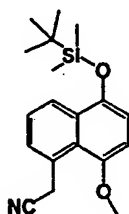


- Compound A56 may be prepared by the methods described for compound A55 by replacing compound A55.12 or compound A55.12b with compound A56.1 or
15 compound A56.1.b, respectively.

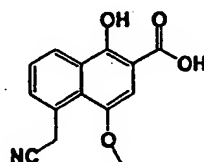


Compound A56.1 Compound A56.1b

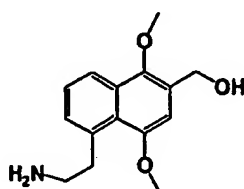
- Compound A56.1 may be prepared by a multi-step process. Naphthalene-1,4-
- 5 diol may be treated with one equivalent of tert-butyldimethylchlorosilane and base in an inert solvent to give 4-(tert-butyl-dimethyl-silanyloxy)-naphthalen-1-ol. Treatment with methyl iodide and base will give tert-Butyl-(4-methoxy-naphthalen-1-yloxy)-dimethyl-silane. Heating with hexacarbonylchromium will form the $\text{Cr}(\text{CO})_3$ complex. Treatment with LiCH_2CN in an inert solvent followed
- 10 by oxidation with iodine will give compound A56.2.



Compound A56.2



Compound A56.3



Compound A56.4

The following references relate to this subject matter: McQuillin F.J., et al., *Transition Metal Organometallics for Organic Synthesis*, Cambridge University Press, 1991, p.187, the contents of which are incorporated herein by reference in their entirety.

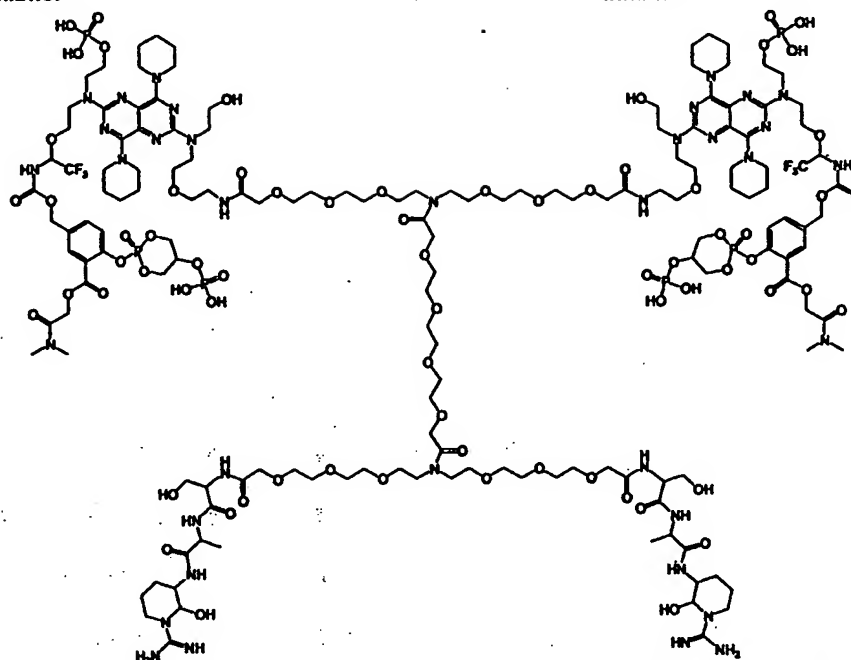
5

The silyl protecting group may be removed with t-butylammonium fluoride and the product may be treated with carbon dioxide and a base such as sodium hydroxide to give compound A56.3. Treatment with methyl iodide and base followed by reduction with lithium aluminum hydride in an inert solvent will give compound A56.4. Treatment with 9-fluorenylmethyl chloroformate in an inert solvent will give compound A56.1b. Treatment of compound A56.1b with chloroacetic anhydride and base, followed by oxidation with cerium (IV) ammonium nitrate in an inert solvent, followed by hydrolysis of the chloroacetate ester will give compound A56.1.

15

Example 57

Example 57 is similar to example 56, however, compound B55 is replaced with compound B57. Compound B57 has two targeting ligands for urokinase and two masked nucleoside transport inhibitors that are based on dipyridamole. The dipyridamole groups are masked with esterase activated clock like time delay triggers. An additional phosphate group on the dipyridamole moiety will be cleaved by phosphatases.

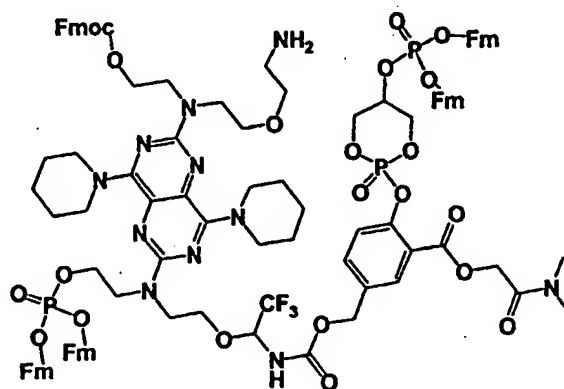
Masked Nucleoside transport
inhibitorMasked Nucleoside transport
inhibitor

Urokinase selective ligand

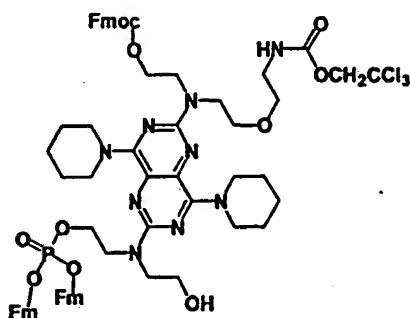
Compound B57

Urokinase selective ligand

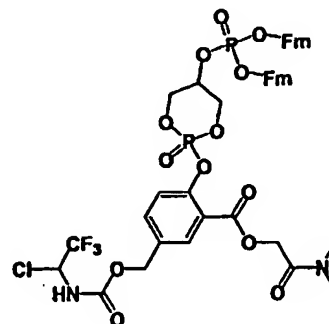
- Compound B57 may be prepared by the method described for compound B55 by
 5 replacing heptylamine with compound B55.2 and also replacing compound B55.4
 with compound B57.1.

**Compound B57.1**

Compound B57.1 may be prepared by reacting compound B57.2 and compound B57.3 in an inert solvent in the presence of base and then cleaving the trichloroethyl ester with Zn and phosphate buffer.



Compound B57.2



Compound B57.3

5

Compound B57.2 may be prepared by a multi-step process. Reacting 2,6-Dichloro-4,8-di-piperidin-1-yl-pyrimido[5,4-d]pyrimidine with (2-[2-(2-(Tetrahydropyran-2-yloxy)-ethylamino)-ethoxy]-ethyl)-carbamic acid 2,2,2-trichloro-ethyl ester in an inert solvent in the presence of base will give compound B57.4. Reacting compound B57.4 with carbonic acid tert-butyl ester 2-[2-(tert-butyl-dimethyl-silyloxy)-ethylamino]-ethyl ester in an inert solvent in the presence of a base will give compound B57.5.

10



10 remove the t-Boc group and give compound B57.2.

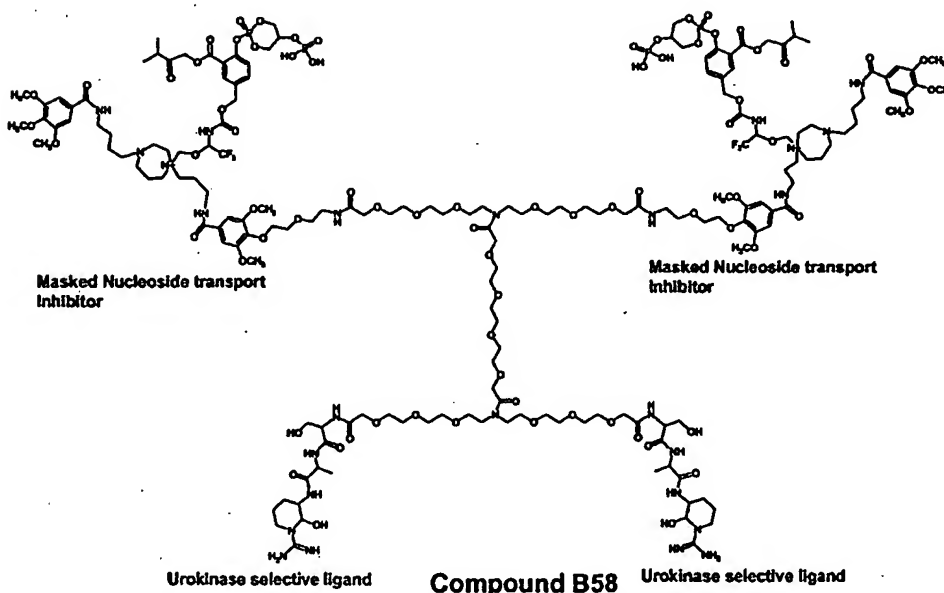
Treatment with one equivalent benzyl chloroformate and pyridine will give (2-Hydroxy-ethyl)-{2-[2-(2,2,2-trichloro-ethoxycarbonylamino)-ethoxy]-ethyl}-carbamic acid benzyl ester. Treatment with acid catalyst and dihydropyran will

give [2-(Tetrahydro-pyran-2-yloxy)-ethyl]-{2-[2-(2,2,2-trichloro-ethoxycarbonylamino)-ethoxy]-ethyl}-carbamic acid benzyl ester. Catalytic hydrogenation with Pd on carbon will give the desired final product.

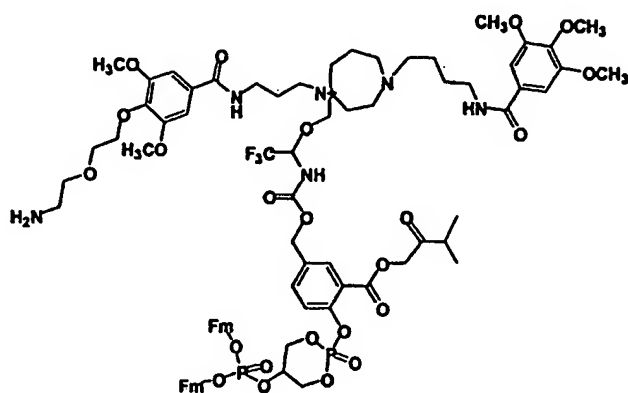
- 5 The compound carbonic acid tert-butyl ester 2-[2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-ethyl ester may be prepared by a multi-step process. Treating 2-(2-Hydroxy-ethylamino)-ethanol with benzyl chloroformate and a base such as pyridine in an inert solvent will give bis-(2-hydroxy-ethyl)-carbamic acid benzyl ester. Treatment with 1 equivalent of tert-butyldimethylchlorosilane and base in an inert solvent will give, after purification, [2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-{2-(2-hydroxy-ethyl)-carbamic acid benzyl ester. Treatment with di-t-butyl pyrocarbonate and base in an inert solvent followed by catalytic hydrogenation with Pd on carbon will give the desired final product.
- 10
- 15 Compound B57.3 may be prepared by a multi-step process. Treating compound 49.9b with acid or a reagent such as tetrabutylammonium fluoride will remove the silyl protecting group. The product may then be reacted with phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester and a base such as triethylamine in an inert solvent. The aldehyde group may then be reduced by
- 20 catalytic hydrogenation with Pd on carbon or with a reagent such as sodium borohydride. The product may then be treated with phosgene in an inert solvent. The product may then be treated with one equivalent of ammonia and a base in an inert solvent. The product may then be treated with trifluoroacetaldehyde. The product may then be treated with a reagent such as phosphorous trichloride
- 25 to give compound B57.3.

Example 58

Example 58 is similar to example 57, however, a different nucleoside transport inhibitor is employed. In compound B58, an analog of dilazep is employed as the
 5 nucleoside transport inhibitor. The dilazep analog is masked with an esterase activated clock like time delayed trigger. In example B58, the amide analog of dilazep is employed. The following references relate to this subject matter: Gati W.P.; Paterson A.R.P., "Interaction of [³H]Dilazep at Nucleoside Transporter-Associated Binding Sites on S49 Mouse Lymphoma Cells," *Molecular*
 10 *Pharmacology*, 3:134-141 (1989), the contents of which are incorporated herein by reference in their entirety.

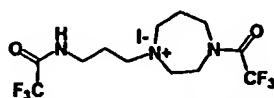


Compound B58 may be employed by the methods described for compound B57 by replacing compound B57.1 with compound B58.1.

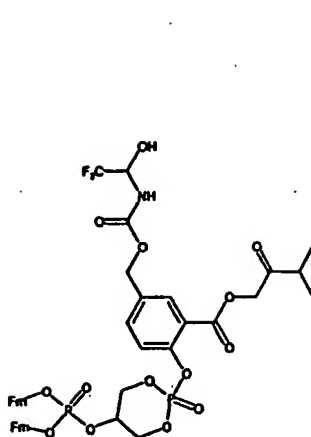
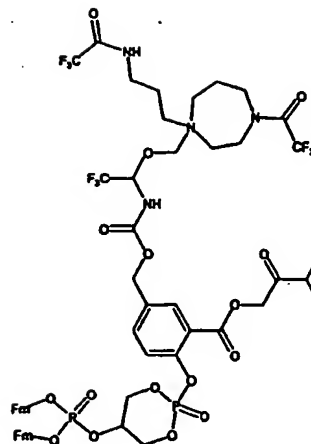
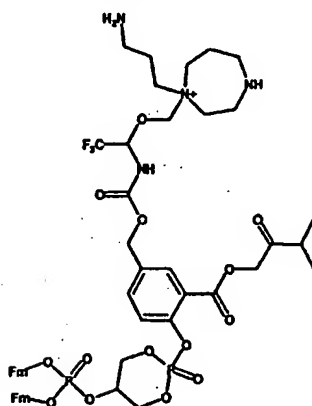
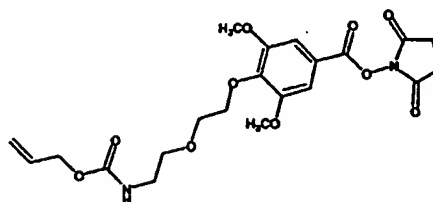
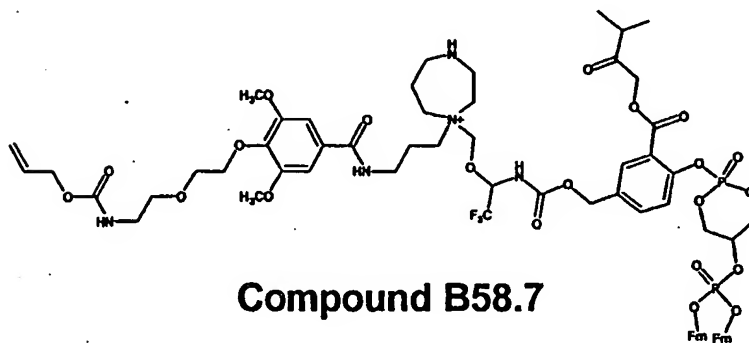


Compound B58.1

- 5 Compound B58.1 may be prepared by a mult-step process. Treating 1,4-diazacycloheptane with toluene-4-sulfonic acid 3-tert-butoxycarbonylamino-propyl ester and base in an inert solvent followed by treatment with acid to remove the t-Boc group will give 3-[1,4]Diazepan-1-yl-propylamine. Treatment with trifluoroacetic anhydride and base will give 2,2,2-Trifluoro-N-{3-[4-(2,2,2-
- 10 trifluoro-acetyl)-[1,4]diazepan-1-yl]-propyl}-acetamide, compound B58.2.
- Treatment of compound B58.3 with iodochloromethane and a base such as N,N-diisopropylethylamine will give the corresponding chloromethyl derivative, which can be reacted with compound B58.2 to give compound B58.4.



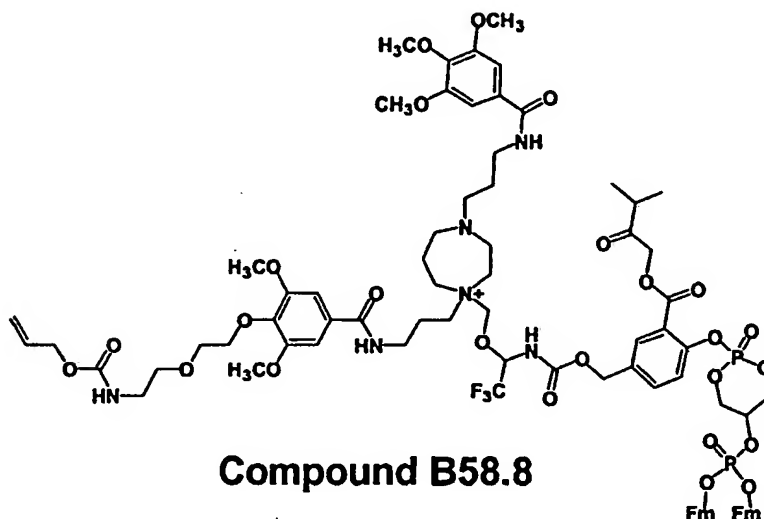
Compound B58.2

**Compound B58.3****Compound B58.4****Compound B58.5****Compound B58.6****Compound B58.7**

Selective removal of the trifluoroacetyl groups with a reagent, such as tris(2-aminoethyl)amine and a transesterification catalyst, such as distannoxane will give compound B58.5. Reacting with compound B58.6 in an inert solvent will

give compound B58.7. Reacting compound B58.7 with 3,4,5-trimethoxy-N-(3-oxo-propyl)-benzamide in an inert solvent, in the presence of acid catalyst with removal of water, followed by reduction with a reagent such as sodium cyanoborohydride will give B58.8.

5



Removal of the alloxycarbonyl protecting group with Pd (0) will give compound B58.1.

10

Compound B58.6 may be prepared by a multi-step process. Treating 2-(2-Amino-ethoxy)-ethanol with di-*t*-butyl pyrocarbonate and in an inert solvent will give [2-(2-Hydroxy-ethoxy)-ethyl]-carbamic acid *tert*-butyl ester. Treating with tosyl chloride and base in an inert solvent will give Toluene-4-sulfonic acid 2-(2-*tert*-butoxycarbonylamino-ethoxy)-ethyl ester. Reacting with 4-Hydroxy-3,5-dimethoxy-benzoic acid *tert*-butyl ester and a strong base will give 4-[2-(2-*tert*-Butoxycarbonyl-amino-ethoxy)-ethoxy]-3,5-dimethoxy-benzoic acid *tert*-butyl ester. Treatment with acid will give 4-[2-(2-Amino-ethoxy)-ethoxy]-3,5-

dimethoxy-benzoic acid. Treatment with allyl chloroformate under Schotten-Bauman conditions followed by coupling to N-hydroxysuccinimide with a reagent such as dicyclohexylcarbodiimide will give compound B58.6.

5

Example 59

Compounds A59, B55, C59 and folic acid are a set of compounds, which when used in combination will exhibit multifactorial targeting with synergistic toxicity against tumor cells that jointly express urokinase, MMP2, 3, 9, 12, and 13, and
10 laminin receptors.

Compound A59 will deliver trimetrexate to laminin receptor positive cells. Trimetrexate is a potent inhibitor of dihydrofolate reductase.

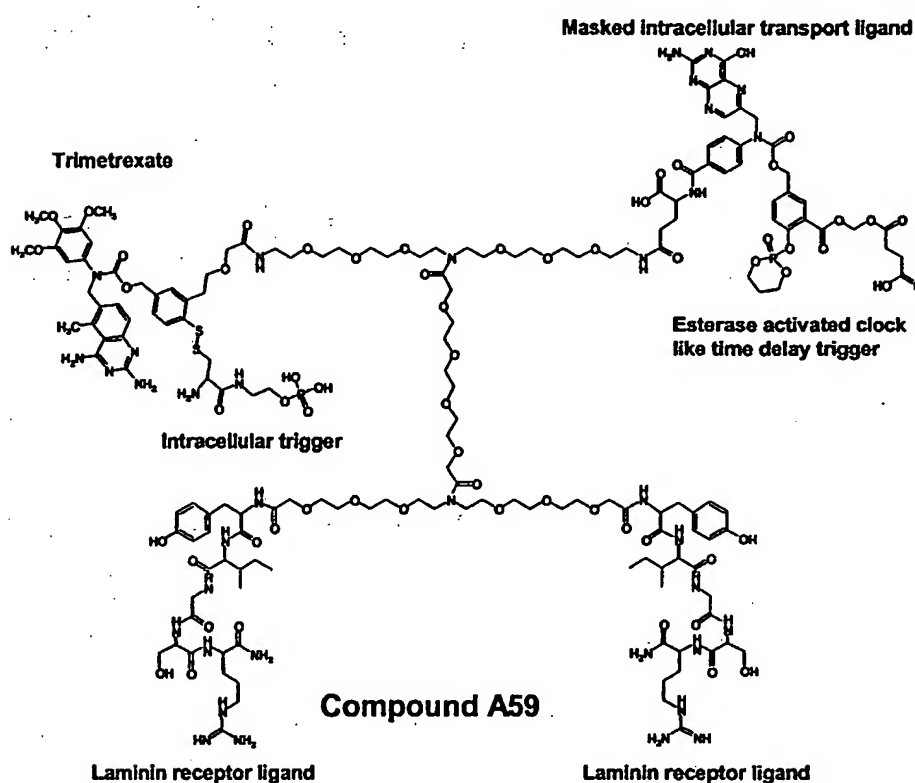
15 Compound B55 will deliver to urokinase positive cells masked "5'-S-(2-Aminoethyl)-N6-(4-Nitrobenzyl)-5'-Thioadenosine ligands, which when unmasked will bind tightly to nucleoside transport proteins on the surface of the targeted cells.

20 Compound C59 will deliver AG2034 to MMP2, 3, 9, 12, and 13 positive cells. AG2034 is a potent inhibitor of glycinamide ribonucleotide formyltransferase.

Pronounced synergistic toxicity is expected in cells that are jointly targeted by compounds A59, B55, and C59 in the presence of exogenous folate. The
25 following references relate to this subject matter: Gaumont Y., et al., "Quantitation of Folic Acid Enhancement of Antifolate Synergism," *Cancer Res*,

52:2228-2235 (1992); Faessel H.M., et al., "Super *in Vitro* Synergy between Inhibitors of Dihydrofolate Reductase and Inhibitors of Other Folate-requiring Enzymes: The Critical Role of Polyglutamylation," *Cancer Res*, 58:3036-3050 (1998), the contents of which are incorporated herein by reference in their

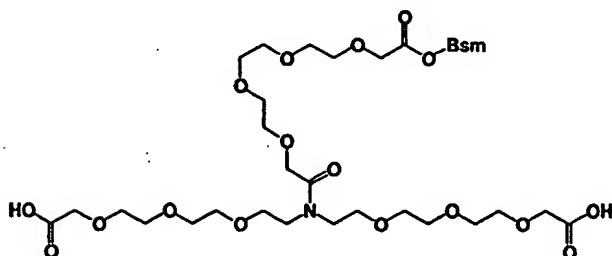
5 entirety.



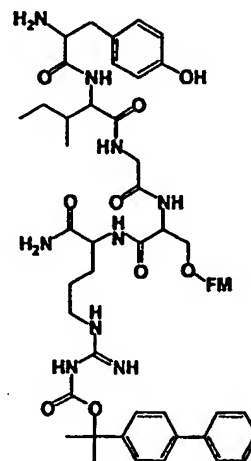
10

Compound A59 may be prepared by a multi-step procedure. Compound A59.1 may be coupled with two equivalents of A59.2. Treatment with tris(2-

aminoethyl)amine under conditions that will leave the Fmoc group intact will cleave the Bsm ester. The product may then be coupled to compound A59.3. Treatment with dilute acid followed by base will then give compound A59.

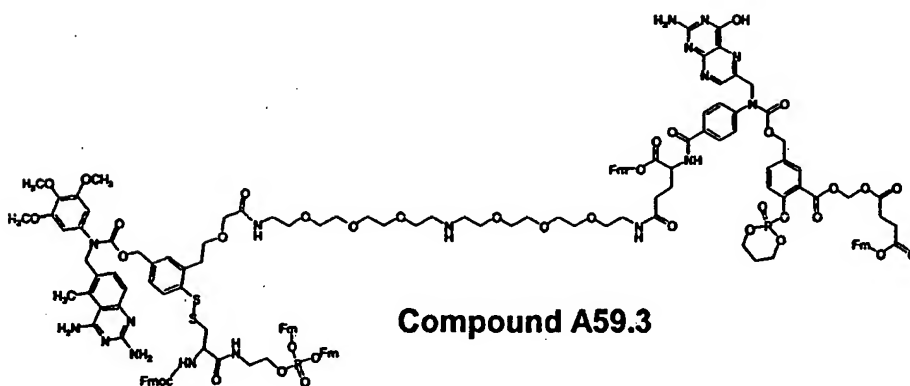


Compound A59.1



Compound A59.2

5



Compound A59.3

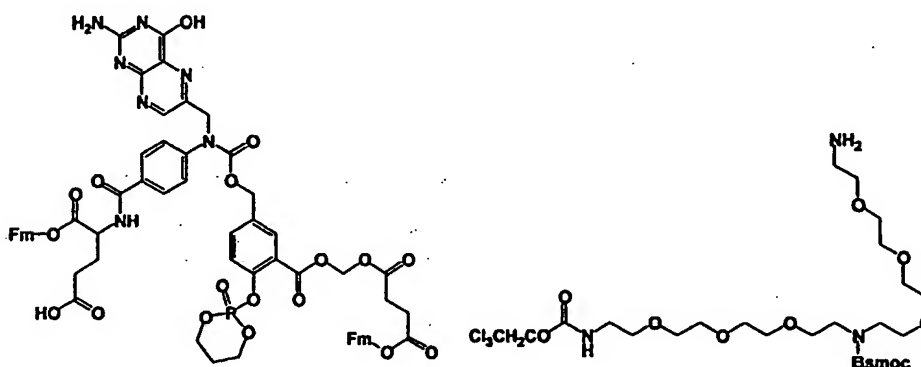
Compound A59.1 may be prepared by coupling compound B55.1a and (2-{2-[2-(1,1-Dioxo-1H-116-benzo[b]thiophen-2-ylmethoxycarbonyl(methoxy)-ethoxy]-ethoxy)-ethoxy)-acetic acid and then cleaving the allyl esters with Pd (0).

10

Compound A59.2 may be prepared by routine methods of oligopeptide synthesis.

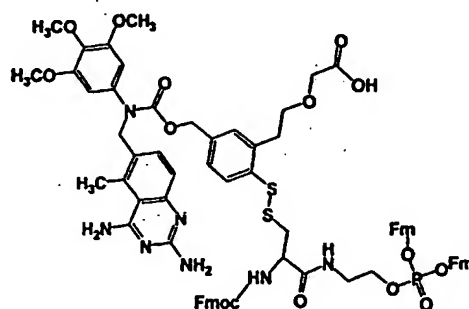
Compound A59.3 may be prepared by coupling compound A59.4 and A59.5, treating with Zn and acid to remove the trichloroethoxycarbonyl protecting group, coupling with A59.6, and then treating with tris(2-aminoethyl)amine under

5 conditions that will leave the Fmoc group intact to remove Bsmoc group.



Compound A59.4

Compound A59.5



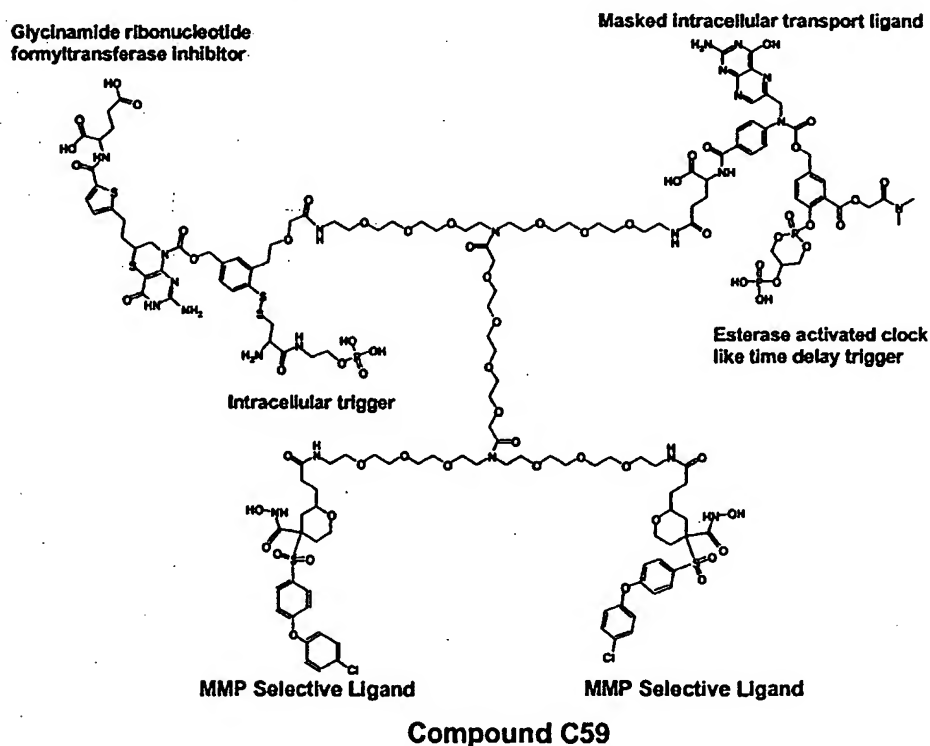
Compound A59.6

The synthesis of compound A59.4 has been given elsewhere. Compound A59.5

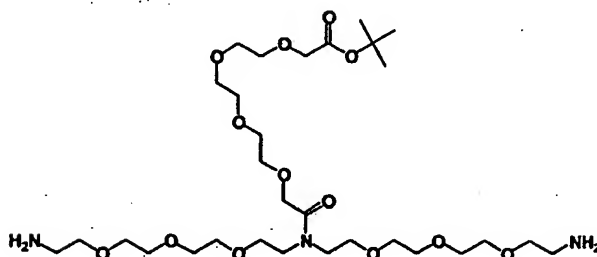
10 may be prepared by a multi-step procedure. Treating Bis-(2-{2-[2-(2-amino-ethoxy)-ethoxy]-ethoxy}-ethyl)-amine with one equivalent of trityl chloride and base in an inert solvent will give, after purification, (2-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-ethyl)-[2-(2-{2-[2-(trityl-amino)-ethoxy]-ethoxy}-ethoxy)-ethyl]-

amine. Treatment with 1 equivalent of carbonic acid 2,5-dioxo-pyrrolidin-1-yl ester 2,2,2-trichloro-ethyl ester will give {2-[2-(2-[2-(2-[2-(2-[2-(Trityl-amino)-ethoxy]-ethoxy)-ethoxy)-ethylamino]-ethoxy)-ethoxy)-ethoxy]-ethyl)-carbamic acid 2,2,2-trichloro-ethyl ester. Treatment with 1 equivalent of (1,1-Dioxo-1H-
 5 1 λ 6-benzo[b]thiophen-2-yl)-methyl chloroformate and base, followed by HCl treatment to remove the trityl group will give compound A59.5.

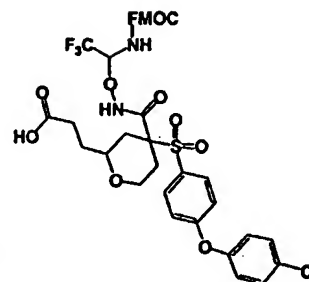
Compound A59.6 may be prepared by reacting trimetrexate and compound 23.2b in an inert solvent in the presence of a base such as pyridine and then
 10 treating with tris(2-aminoethyl)amine under conditions that will leave the Fmoc group intact to cleave the Bsm ester.



Compound C59 may be prepared by a multistep procedure. Compound C59.1 may be coupled with two equivalents of compound C59.2.

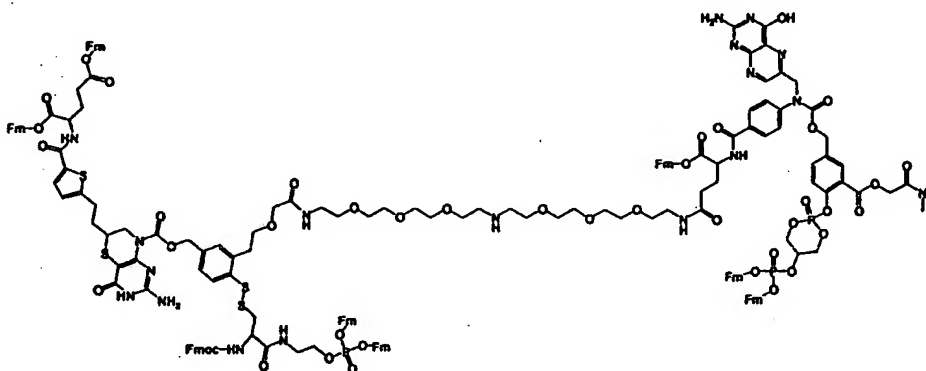


Compound C59.1



Compound C59.2

Treatment with trifluoroacetic acid will remove the t-butyl ester. The product may then be coupled to compound C59.3. Treatment with base will then give compound C59.



Compound C59.3

Compound C59.1 may be prepared by a multi-step process. The compound 2-(2-(2-(Trityl-amino)-ethoxy)-ethoxy)-ethylamine may be coupled to {2-[2-(2-Benzoyloxycarbonylamino-ethoxy)-ethoxy]-ethoxy}-acetic acid. The product may then be reduced with a reagent such as lithium aluminum hydride in an inert solvent. The product may then be treated with trityl chloride and base in an inert

solvent to give Bis-[2-(2-[2-(2-(trityl-amino)-ethoxy)-ethoxy]-ethoxy)-ethyl]-amine.

This may then be coupled to {2-[2-(2-tert-Butoxycarbonylmethoxy-ethoxy)-ethoxy]-ethoxy}-acetic acid and treated with dilute acid to remove the trityl groups to give compound C59.1.

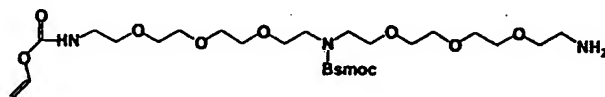
5

The synthesis of compound C59.2 was given in example 17.

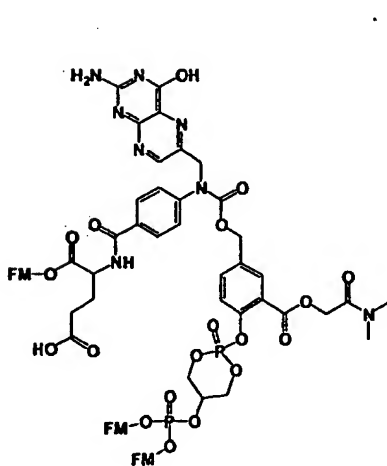
Compound C59.3 may be prepared by a multi-step procedure. Compound

C59.4 may be coupled to compound C59.5. Treatment with Pd(0) will remove

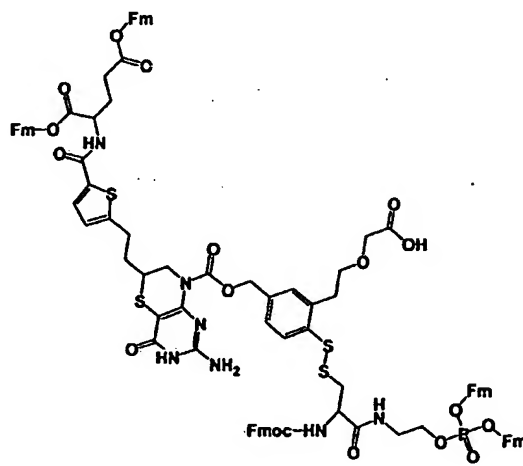
10 the allyloxycarbonyl protecting group. The product may then be coupled with compound C59.6. Treatment with tris(2-aminoethyl)amine under conditions that will leave the Fmoc group intact will give compound C59.3.



Compound C59.4



Compound C59.5

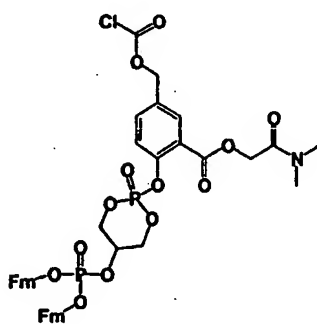


Compound C59.6

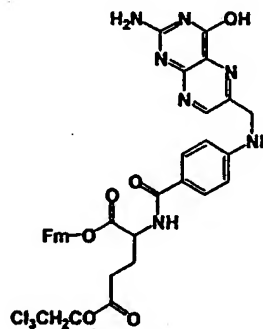
15

Compound C59.4 may be prepared by a multi-step process. Treating Bis-(2-{2-[2-(2-amino-ethoxy)-ethoxy]-ethoxy}-ethyl)-amine with 1 equivalent of trityl chloride and isolating the monosubstituted product will give (2-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-ethyl)-[2-(2-{2-[2-(trityl-amino)-ethoxy]-ethoxy}-ethoxy)-ethyl]-amine. Treating with one equivalent of a reagent such as carbonic acid allyl ester 2,5-dioxo-pyrrolidin-1-yl ester in an inert solvent, followed with (1,1-Dioxo-1H-1λ6-benzo[b]thiophen-2-yl)-methyl chloroformate and base, followed by HCL treatment to remove the trityl group will give compound C59.4 as the hydrochloride salt.

Compound C59.5 may be prepared by reacting C59.5a and C59.5b in an inert solvent in the presence of a base such as pyridine and then treating with Zn and acid to remove the trichloroethyl group.



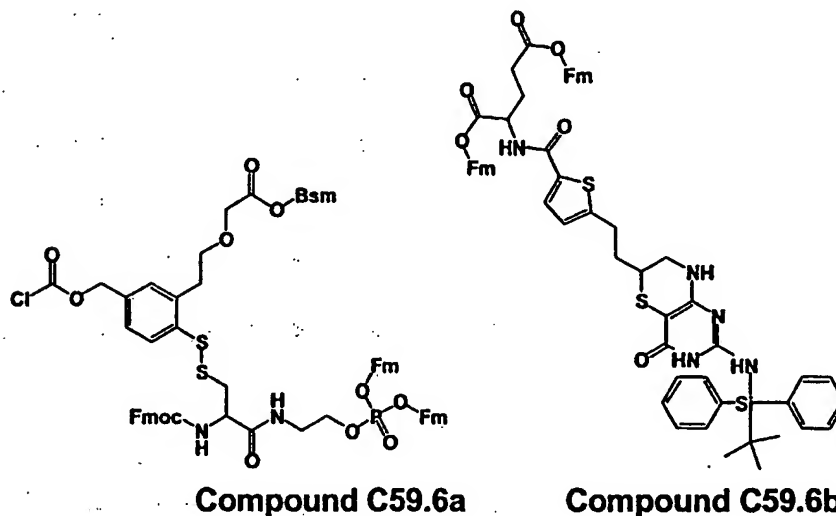
Compound C59.5a



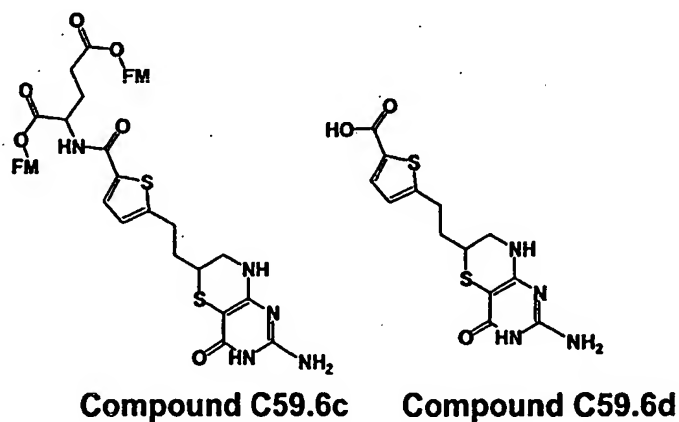
Compound C59.5b

Compound C59.6 may be prepared by coupling reacting compound C59.6a and compound C59.6b in an inert solvent in the presence of a base followed by removal of the silyl and Bsm protecting groups. The silyl based protecting group

may be removed by a reagent such as pyridine HF. The Bsm ester may be selectively cleaved with tris(2-aminoethyl)amine under conditions that will leave the Fmoc group intact.



- 5 Compound C59.6b may be prepared by treating compound C59.6c with tert-butylchlorodiphenylsilane in an inert solvent in the presence of base. Compound C59.6c may be prepared by coupling compound C59.6d and L-glutamic acid di-(9H-Fluoren-9-yl)-methyl ester. Compound C59.6d is a known compound.



- 10 The following references relate to this subject matter: Varney M.D., et al.,
 "Protein Structure-Based Design, Synthesis, and Biological Evaluation of 5-Thia-
 2,6-diamino-4(3H)-oxypyrimidines: Potent Inhibitors of Glycinamide

Ribonucleotide Transformylase with Potent Cell Growth Inhibition," *J Med Chem*,
40:2502-2524 (1997); Overman L.E., et al., "tert-Butyldiphenylsilylamines: A
Useful Protecting Group for Primary Amines," *Tetrahedron Let*, 27(37):4391-
4394 (1986), the contents of which are incorporated herein by reference in their
5 entirety.

Example 60

Compounds A59, B57, C59 and folic acid are a set of compounds which when
10 used in combination will exhibit multifactorial targeting against tumor cells that
jointly express urokinase, MMP2, 3, 9, 12, and 13, and laminin receptors.

Example 61.1

15 Compounds A59, B58, C59 and folic acid are a set of compounds, which when
used in combination, will exhibit multifactorial targeting against tumor cells that
jointly express urokinase, MMP2, 3, 9, 12, and 13, and laminin receptors.

20

Example 61.2

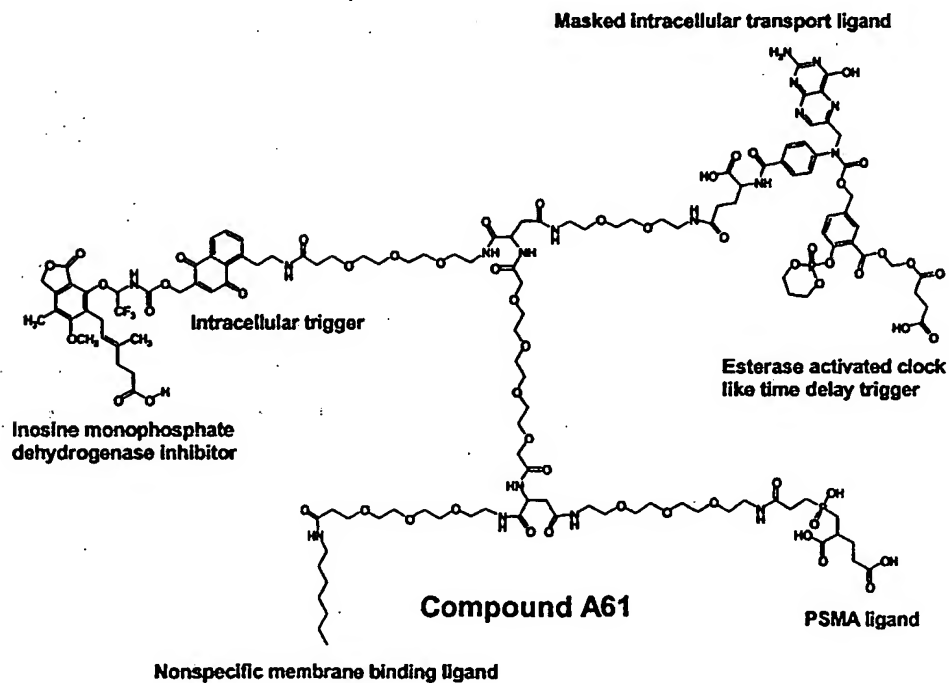
Compounds A61, B57, and C61 are a set of compounds, which when used in
combination, will exhibit targeting against tumor cells that jointly express
25 urokinase, and PSMA or MMP(2, 3, 9, 12, or 13) and PSMA. Compound A61

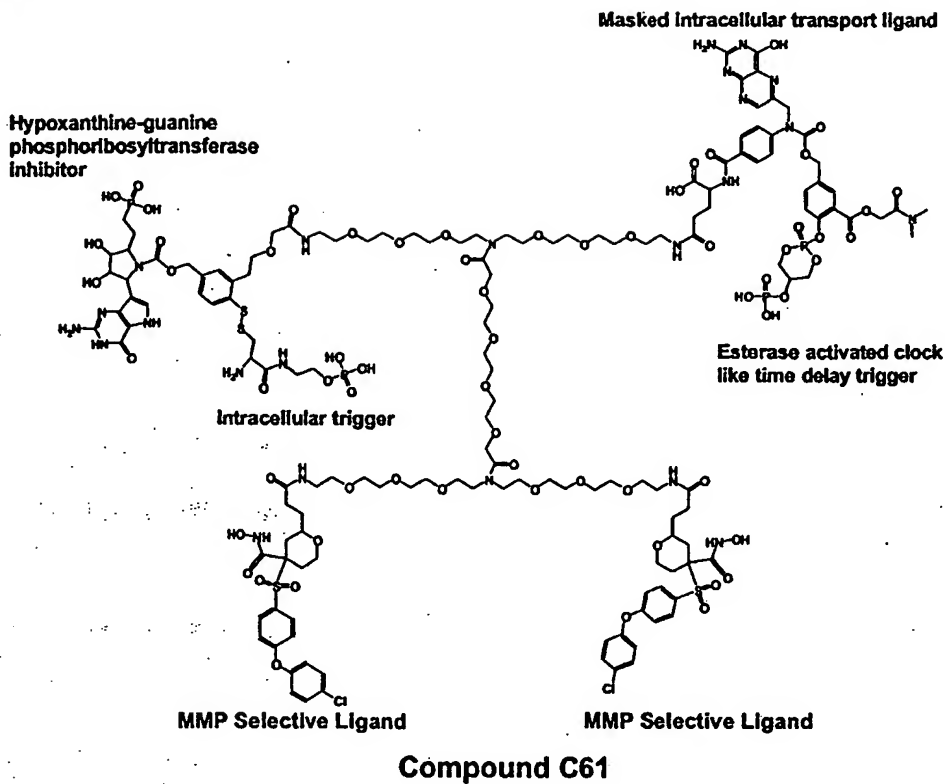
will deliver mycophenolic acid, a potent inhibitor of inosine monophosphate dehydrogenase, to PSMA positive cells. Compound B57 will deliver a nucleoside transport inhibitor based on dipyridamole to the surface of urokinase positive cells.

5

Compound C61 will deliver an ImmucillinGP analog to MMP 2, 3, 9, 12 or 13 positive cells. ImmucillinGP is a potent inhibitor of hypoxanthine-guanine phosphoribosyltransferase. Jointly targeted cells will be exposed to inhibitors of both the denovo and salvage pathways of guanine nucleotide synthesis.

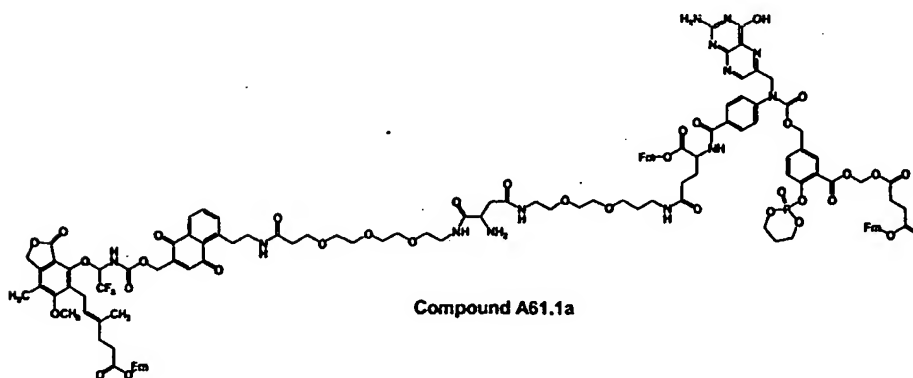
10



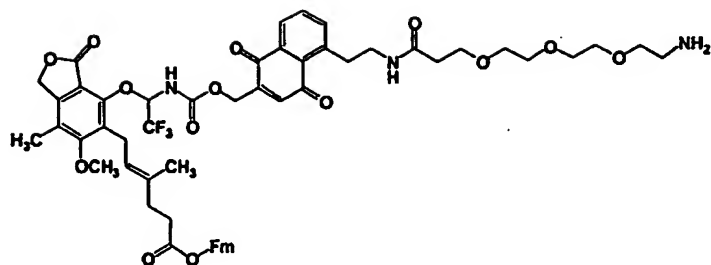
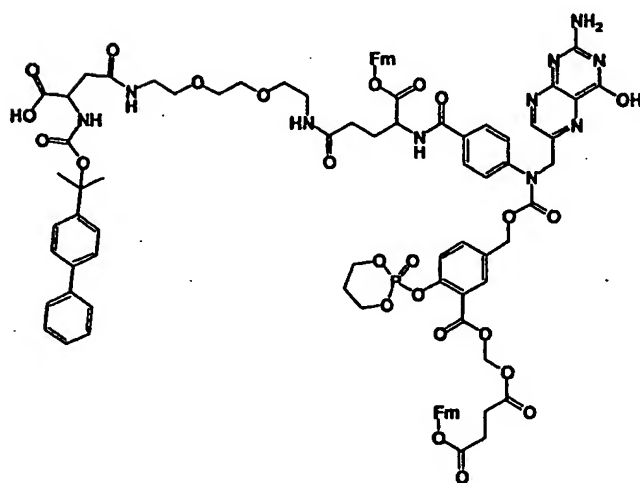


Compound A61 may be prepared by coupling compound A55.5 and compound

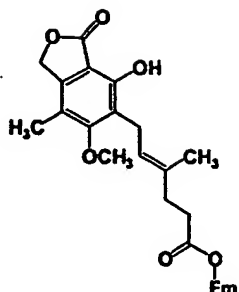
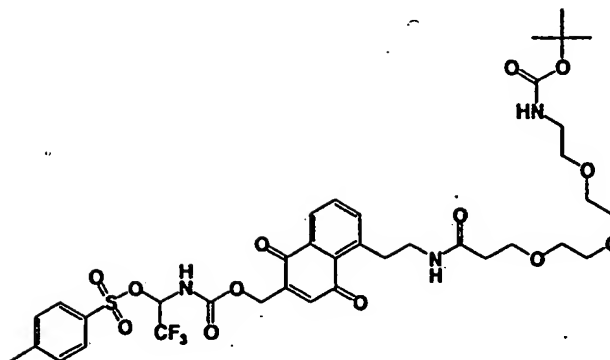
5 A61.1a.



Compound A61.1a may be prepared by coupling compound A61.1 b and compound A61.1c and then treating with acid to remove the 2-Biphenyl-4-yl-propan-2-oxy-carbonyl protecting group.

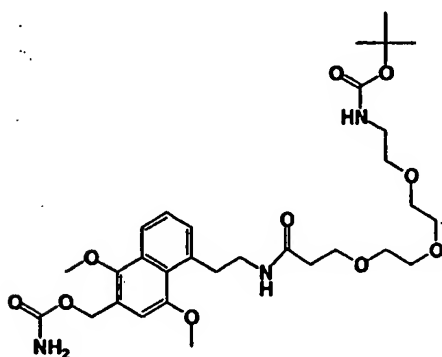
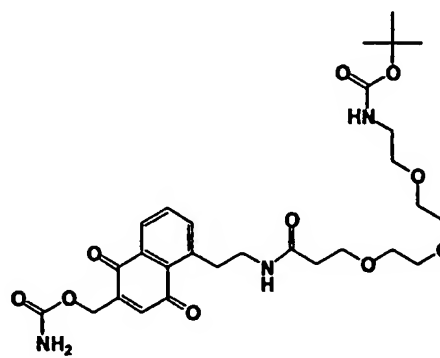
**Compound A61.1b****Compound A61.1c**

- Compound A61.1b may be prepared by reacting compound A61.2 and
- 5 compound A61.3 in the presence of base in an inert solvent and then treating with acid to remove t-Boc group.

**Compound A61.2****Compound A61.3**

Compound A61.2 may be prepared by treating mycophenolic acid with (9H-Fluoren-9-yl)-methanol and an agent such as dicyclohexylcarbodiimide in an inert solvent. Alternatively the phenol hydroxyl may be protected before esterification.

Compound A61.3 may be prepared by a multi-step process. Compound A56.4 may be coupled with 3-{2-[2-(2-tert-Butoxycarbonylamino-ethoxy)-ethoxy]-ethoxy}-propionic acid in an inert solvent. The product may then be treated with phosgene and a base such as pyridine, followed by ammonia at low temperature to give compound A61.4.

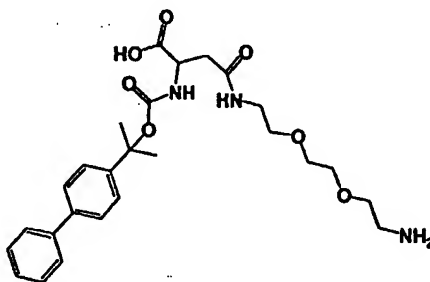
**Compound A61.4****Compound A61.5**

Compound A61.4 may be treated with cerium (IV) ammonium nitrate in an inert solvent to give compound A61.5. Treatment of compound A61.5 with trifluoroacetaldehyde followed by tosyl chloride and base in an inert solvent will

5 give compound A61.3.

Compound A61.1c may be prepared by treating compound 32.1 with N-hydroxysuccinimide and dicyclohexylcarbodiimide to form the active ester, and then reacting the product with compound A61.6 in an inert solvent in the

10 presence of base.



Compound A61.6

Compound A61.6 (as the salt) may be prepared by coupling L- N-(2-Biphenyl-4-yl-propan-2-oxy-carbonyl) aspartic acid α methyl ester with 2-[2-(2-Amino-

15 ethoxy)-ethoxy]-ethylamine and then cleaving the methyl ester with base.

Compound C61 may be prepared by the method described for compound C59 by replacing compound C59.6b with compound 20.9.

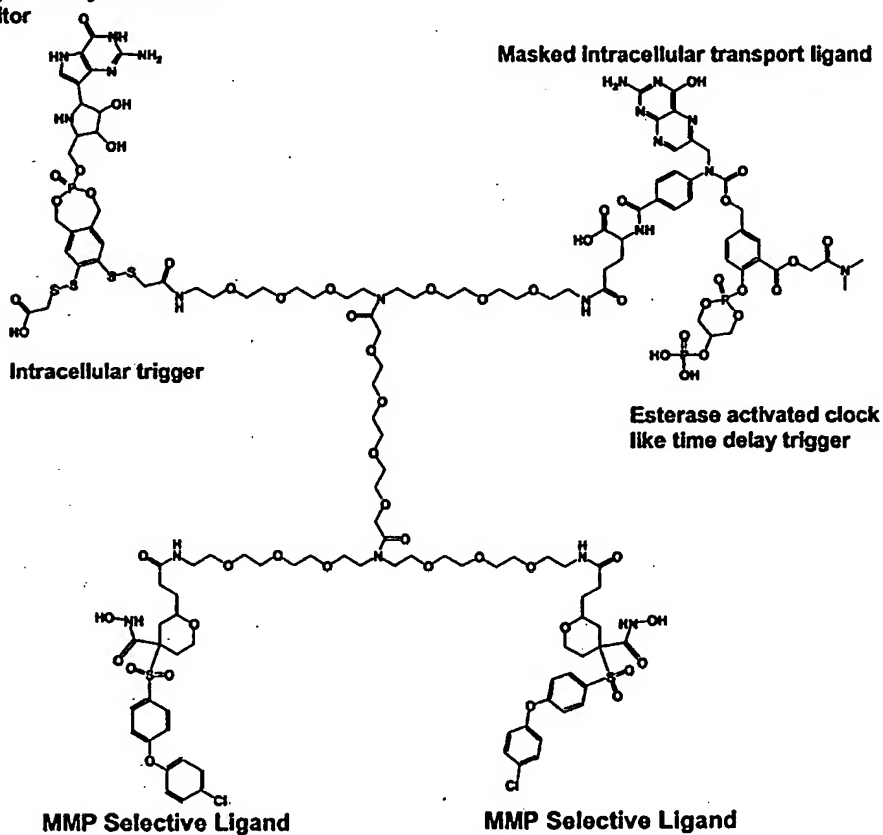
20

Example 62

Compounds A61, B57, and C62 are a set of compounds, which when used in combination, will exhibit targeting against tumor cells that jointly express urokinase, and PSMA or MMP(2, 3, 9, 12, or 13) and PSMA. Compound C62 is similar to compound C61 except that ImmucillinGP, rather than the phosphonate analog of ImmucillinGP, is employed. Also, a different intracellular trigger is employed.

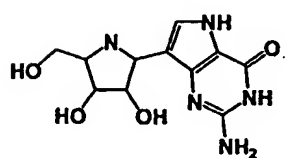
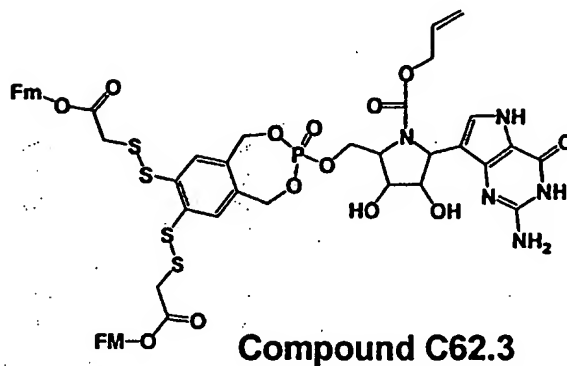
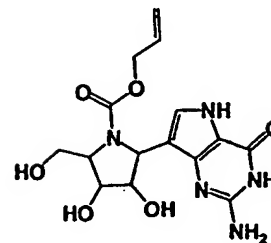
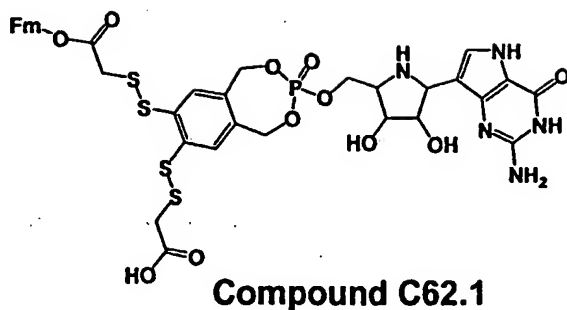
Hypoxanthine-guanine
phosphoribosyltransferase
inhibitor

Masked intracellular transport ligand



Compound C62

- 10 Compound C62 may be prepared by the method described for compound C59 by replacing compound C59.6 with compound C62.1.



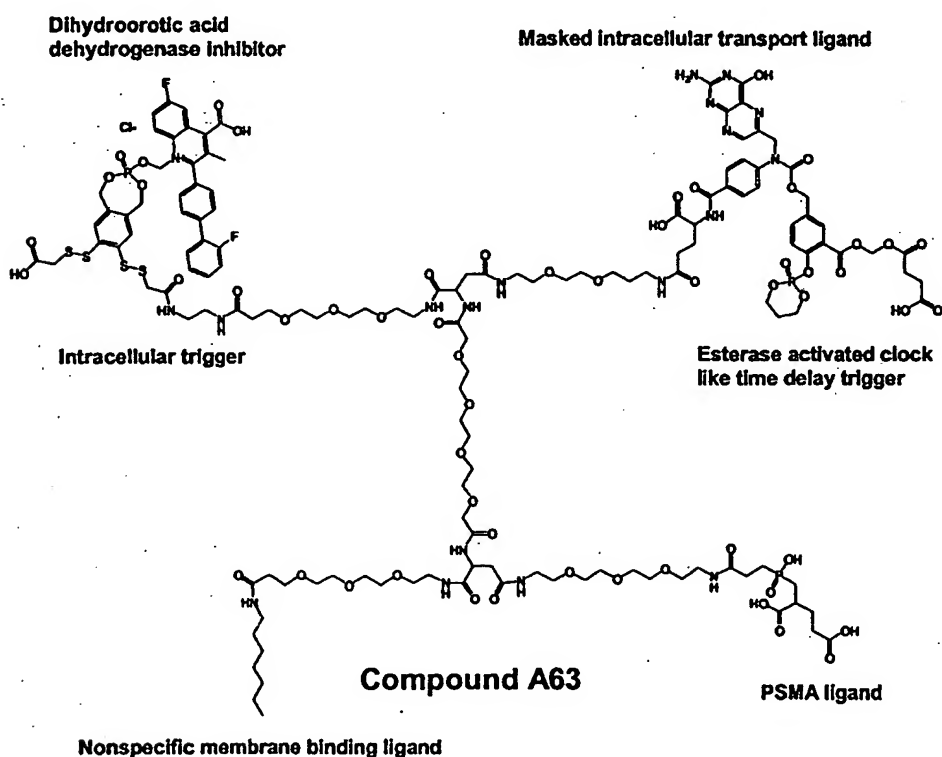
- 5 Compound C62.1 may be prepared by reacting compound C62.2 and compound 42.2 in an inert solvent in the presence of base, to give compound C62.3.

Treatment with one equivalent of strong base, followed by removal of the allyloxycarbonyl protecting group with Pd(0), will give compound C62.1.

- 10 Compound C62.2 may be prepared by treating compound C62.4 with one equivalent of allyl chloroformate and base in an inert solvent.

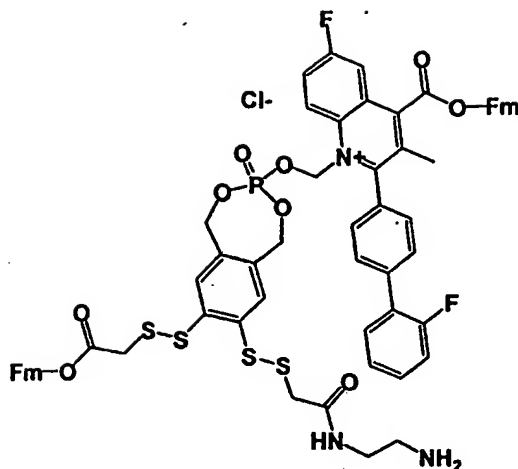
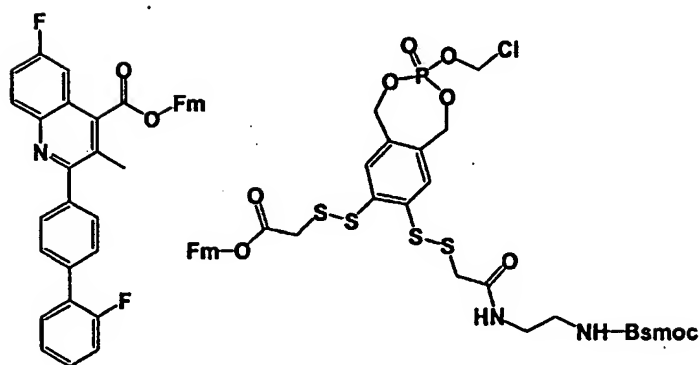
Example 63

Compound A63 and compound B55 are a set of compounds that will selectively target cells that are positive for both urokinase and PSMA. Compound A63 will deliver brequinar, a potent inhibitor of dihydroorotic acid dehydrogenase to PSMA positive cells. Dihydroorotic acid dehydrogenase is the fourth enzyme in the committed pathway of de novo pyrimidine synthesis. Compound B55 will deliver to urokinase positive cells a nucleoside transport inhibitor.



10

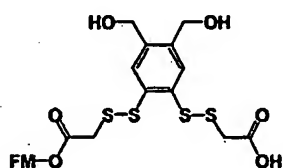
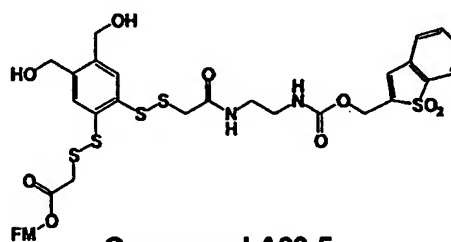
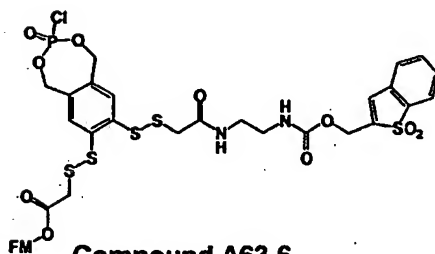
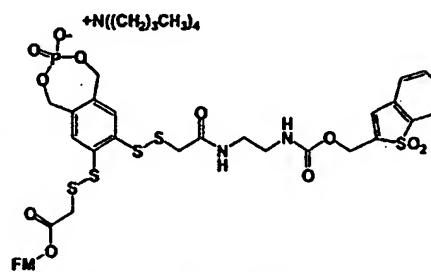
Compound A63 may be prepared by the method described for compound A55 by replacing compound A55.9 with compound A63.1.

**Compound A63.1****Compound A63.2****Compound A63.3**

Compound A63.1 may be prepared by a multi-step process. Reacting A63.2 and A63.3 in an inert solvent followed by removal of the Bsm group with tris(2-aminoethyl)amine under conditions that will leave the Fmoc group intact will give compound A63.1.

Compound A63.2 may be prepared by reacting brequinar with (9H-Fluoren-9-yl)-methanol and dicyclohexylcarbodiimide in an inert solvent.

Compound A63.3 may be prepared by a multi-step process. Compound 42.3 may be treated with one equivalent of a strong base to give compound A63.4. This may then be coupled to (2-Amino-ethyl)-carbamic acid 1,1-dioxo-1H-11,6-benzo[b]thiophen-2-ylmethyl ester to give compound A63.5. Treatment with phosphorous oxychloride and base will give compound A63.6. Treatment with one equivalent of tetrabutylammonium hydroxide in an inert solvent at low temperature will give compound A63.7. Treatment with iodochloromethane and base in an inert solvent will give A63.3.

**Compound A63.4****Compound A63.5****Compound A63.6****Compound A63.7**

15 Example 64

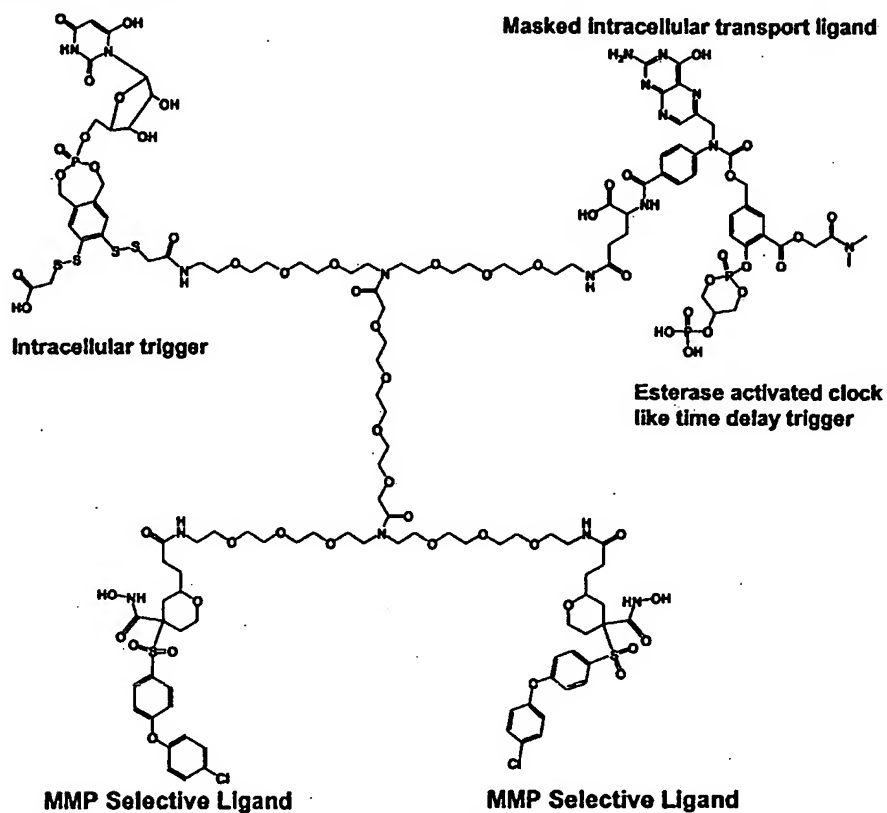
Compound A64 and compound B55 are a set of compounds that will target cells that express MMP (2, 3, 9, 12, or 13) and urokinase. Compound A65 will deliver

to MMP + cells a potent inhibitor to Orotidine 5'-phosphate decarboxylase. This enzyme catalyzes the final step in the de novo synthesis of uridine monophosphate. Compound B55 will deliver to urokinase positive cells a nucleoside transport inhibitor.

5

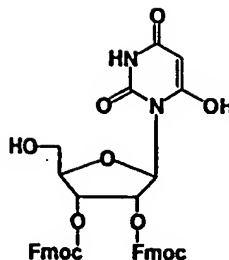
Orotidine-5'-phosphate
decarboxylase inhibitor

Masked intracellular transport ligand



Compound A64

Compound A64 may be prepared by the method described for compound C62 by
10 replacing compound C62.4 with compound A64.1.



Compound A64.1

Compound A64.1 may be prepared by treating the parent nucleoside with one equivalent of trityl chloride and base in an inert solvent followed by two equivalents of 9-fluorenylmethyl chloroformate and a base such as pyridine, followed by treatment with acid to remove the 5' trityl group. The following references relate to this subject matter: Levine H.L., et al., "Inhibition of Orotidine-5'-phosphate Decarboxylase by 1-(5'-Phospho-β-D-ribofuranosyl)barbituric Acid, 6-Azauidine 5'-Phosphate, and Uridine 5'-Phosphate," *Biochemistry*, 19:4993-4999 (1980), the contents of which are incorporated herein by reference in their entirety.

Example 65

Compound A65 has targeting ligands for urokinase, MMP (2, 3, 9, 12, or 13) and sigma receptors. The multifunctional delivery vehicle will deliver hydroxystaurosporine following intracellular transport and activation of an intracellular trigger by thiol reductases and cleavage of the phosphate ester by phosphatases. Hydroxystaurosporine or UCN-01 is a potent inhibitor of protein kinases and exhibits synergistic toxicity with a wide range of antineoplastic compounds. The following references relate to this subject matter: Senderowicz A.M.; Sausville E.A., "Preclinical and Clinical Development of Cyclin-Dependent

Kinase Modulators," *J Nat Cancer Institute*, 92(5):376-387 (2000); Bunch R.T.;

Eastman A., "Enhancement of Cisplatin-induced Cytotoxicity by 7-

Hydroxystaurosporine (UCN-01), a New G₂-Checkpoint Inhibitor," *Clin Cancer*

Res, 2:791-797 (1996); Shao R.G., et al., "7-Hydroxystaurosporine (UCN-01)

5 Induces Apoptosis in Human Colon Carcinoma and Leukemia Cells

Independently of p53," *Exp Cell Res*, 234:388-397 (1997); Monks A., et al.,

"UCN-01 Enhances the In Vitro Toxicity of Clinical Agents in Human Tumor Cell

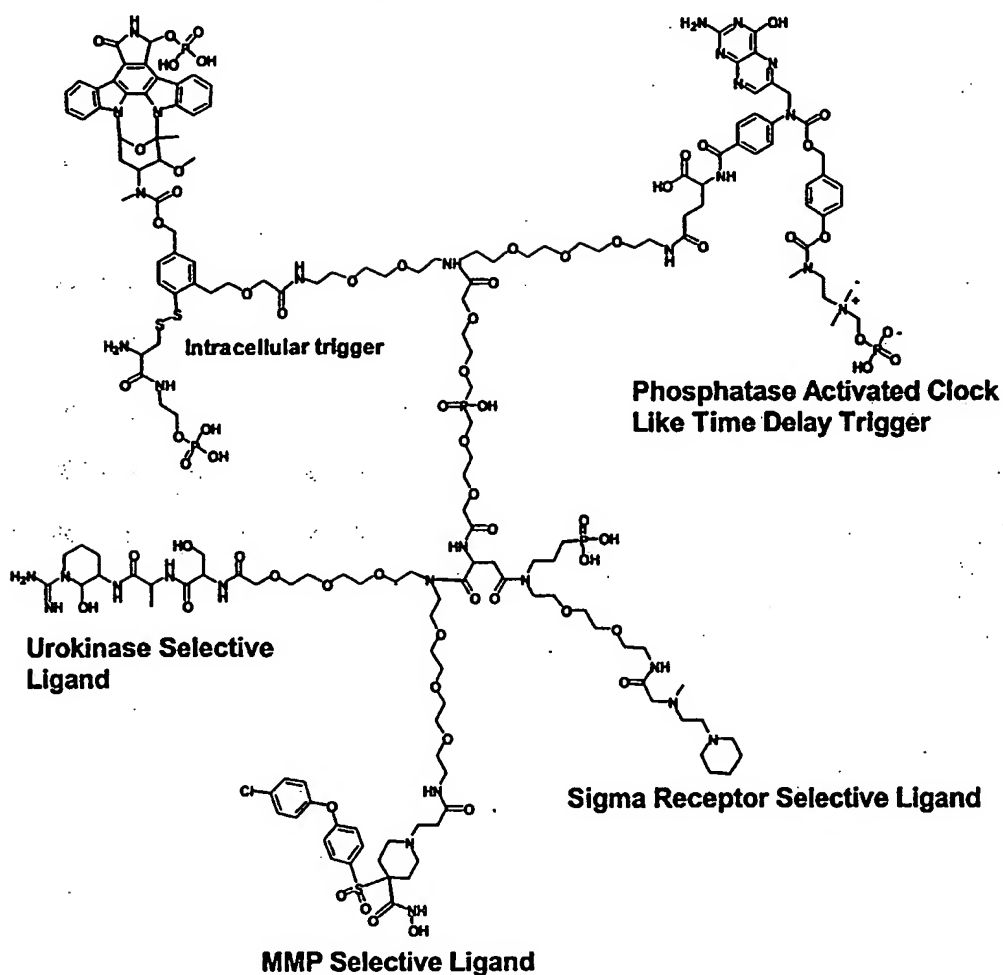
Lines," *Invest New Drugs*, 18(2):95-107 (2000); Takahashi I., et al., "UCN-01 and

UCN-02, New Selective Inhibitors of Protein Kinase C. II. Purification, Physico-

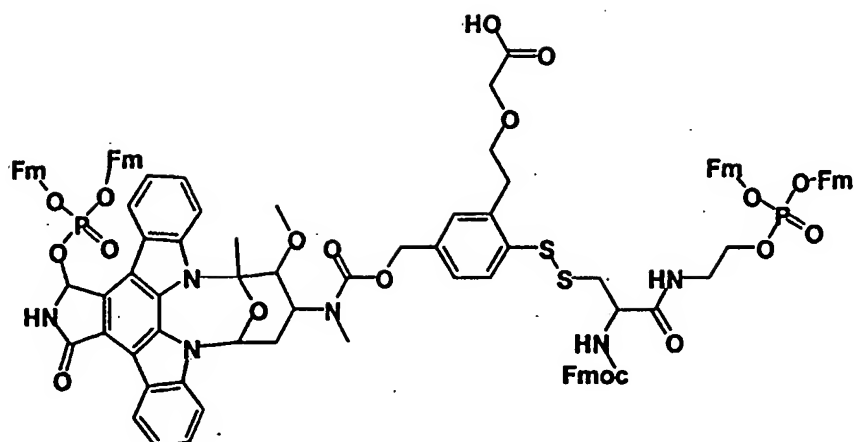
10 chemical Properties, Structural Determination and Biological Activities," *J*

Antibiot, 42(4):571-6 (1989), the contents of which are incorporated herein by

reference in their entirety.

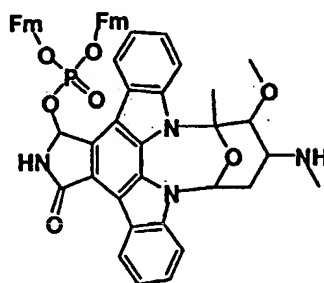
Hydroxystaurosporine**Masked intracellular
transport ligand****Compound A65**

Compound A65 may be prepared by the methods described for compound 50 by replacing compound 50.1 with compound A65.1.



Compound A65.1

- Compound A65.1 may be prepared by reacting compound A65.2 and compound 23.2b in an inert solvent in the presence of a base such as pyridine and then cleaving the Bsm ester with tris(2-aminoethyl)amine under conditions that will
- 5 leave the Fmoc groups intact.



Compound A65.2

- Compound A65.2 may be prepared by treating hydroxystaurosporine (UCN-01) with di-*t*-butyl pyrocarbonate and in an inert solvent and then reacting the product with phosphorochloridic acid bis-(9H-fluoren-9-ylmethyl) ester and a
- 10 base such as triethylamine, and then treating with trifluoroacetic acid to remove the *t*-Boc group.

CLAIMS

What is claimed is:

- 1.) A compound ET in which E is comprised of one or more effector agents having
5 pharmacological activity designated as "PA" and wherein T comprises:
 - a) A group referred to as a "targeting ligand" which selectively binds to a target
receptor on the surface of the target cell or in the microenvironment of the
target cell; and
 - b) One or more of the following:
 - 10 I. A targeting ligand which selectively binds to a target receptor on the
surface of the target cell or in the microenvironment of the target cell;
 - II. A group, referred to as a "masked intracellular transport ligand" which
can be modified in vivo to give a group referred to as an "intracellular
transport ligand" which binds to a target cell receptor that actively
15 transports bound ligands into the target cell;
 - III. A group, referred to as a "trigger" that can be modified in vivo, wherein
in vivo modification activates the trigger and modulates the
pharmacological activity PA;
 - IV. A group, referred to as an "intracellular trapping ligand", which binds to
20 one or more intracellular receptors or a group referred to as a "masked
intracellular trapping ligand" which can be modified in vivo to give an
"intracellular trapping ligand";

and wherein when a second targeting ligand is present in T then the first and second targeting ligands can bind simultaneously to two targeting receptor molecules;

- 5 and wherein when T consists of a targeting ligand and a trigger, and when in vivo modification of the trigger increases the pharmacological activity PA, the in vivo modification which activates the trigger is caused by an enzyme or enzymatic activity that is increased at target cells or decreased at nontarget cells;
- 10 and wherein when T consists of a targeting ligand and a trigger, and when in vivo modification of the trigger decreases the pharmacological activity PA, the in vivo modification which activates the trigger is caused by an enzyme or enzymatic activity that is decreased at target cells or increased at nontarget cells;
- 15 and provided that T is not an antibody, or an analog or component of an antibody, or a complex of antibodies, or a bispecific antibody, or an analog of a bispecific antibody, or a natural protein, or a complex of natural proteins, or a protein, or a naturally occurring polymer, or a radiolabelled dimer, or a polymer to which is attached at multiple sites one or more pharmacologically active compounds that
- 20 evoke the same pharmacological activity PA.

2.) A compound of claim 1 in which the targeting ligand selectively binds to a target receptor on the surface of the target cell or in the microenvironment of the target cell wherein the concentration of the target receptor is greater on the surface of the

target cell or in the microenvironment of the target cell than on the surface or in the microenvironment of nontarget cells.

3.) A compound of claim 2 in which two targeting ligands selectively bind to target
5 receptors on the surface of the target cell or in the microenvironment of the target cell, wherein the concentration of the target receptors is greater on the surface of the target cell or in the microenvironment of the target cell than on the surface or in the microenvironment of nontarget cells.

10 4.) A compound of claim 3 in which the targeting ligands are different and bind to different types of targeting receptors.

5.) A compound of claim 2 in which three targeting ligands selectively bind to target
15 receptors on the surface of the target cell or in the microenvironment of the target cell wherein the concentration of the target receptors is greater on the surface of the target cell or in the microenvironment of the target cell than on the surface or in the microenvironment of non target cells.

6.) A compound of claim 5 in which the targeting ligands are different and bind to
20 different types of targeting receptors.

7.) A compound of claim 1 comprised of two or more targeting ligands wherein at least one of the targeting ligands binds to a target receptor on the surface of the target cell or in the microenvironment of the target cell, wherein the target has an

increased amount of that target receptor compared to a nontarget cell that binds to a second targeting ligand of the compound.

8.) A compound of claim 7 with two different targeting ligands that bind to two
 5 different targeting receptors.

9.) A compound of claim 7 with three different targeting ligands that bind to three
 different targeting receptors.

10 10.) A compound ET of claim 1 comprised of the following groups:
 I. N1 targeting ligands which may differ; and
 II. N2 masked intracellular transport ligands which may differ; and
 III. N3 triggers, which may differ, designated "detoxification triggers", wherein
 activation of the trigger decreases the pharmacological activity PA; and
 15 IV. N4 effector agents which may differ; and
 V. N5 triggers which may differ, wherein activation of the trigger increases the
 pharmacological activity PA; and
 VI. N6 intracellular trapping ligands or masked intracellular trapping ligands,
 which may differ;

20 and wherein:

N1 = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or about 10 N2 = 0, 1, 2, 3, 4, or 5 or about 5

N3 = 0, 1, 2, 3, 4, 5 or about 5 N4 = 1, 2, 3, 4, 5 or about 5

N5 = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or about 10

N6 = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or about 10

11.) A compound of claim 10 in which:

N1 = 1, 2, 3, or 4

N2 = 0, 1, or 2

N3 = 0, 1, or 2

N4 = 1, 2, or 3

N5 = 0, 1, 2, or 3

N6 = 1, 2, or 3

5

12.) A compound of claim 10 wherein:

N1=1, N2=0, N3=1, N4=1, N5=0, and N6=0;

N1=1, N2=0, N3=0, N4=2, N5=0, and N6=0;

N1=1, N2=0, N3=0, N4=3, N5=0, and N6=0;

10 N1=1, N2=0, N3=0, N4=1, N5=1, and N6=0;

N1=1, N2=0, N3=0, N4=1, N5=2, and N6=0;

N1=1, N2=0, N3=0, N4=1, N5=3, and N6=0;

N1=1, N2=0, N3=0, N4=1, N5=0, and N6=1;

N1=1, N2=0, N3=1, N4=2, N5=0, and N6=0;

15 N1=1, N2=0, N3=1, N4=3, N5=0, and N6=0;

N1=1, N2=0, N3=1, N4=1, N5=1, and N6=0;

N1=1, N2=0, N3=1, N4=1, N5=2, and N6=0;

N1=1, N2=0, N3=1, N4=1, N5=3, and N6=0;

N1=1, N2=0, N3=1, N4=1, N5=0, and N6=1;

20 N1=1, N2=0, N3=1, N4=2, N5=1, and N6=0;

N1=1, N2=0, N3=1, N4=2, N5=1, and N6=1;

N1=1, N2=0, N3=1, N4=2, N5=2, and N6=0;

N1=1, N2=0, N3=1, N4=2, N5=2, and N6=1;

N1=1, N2=0, N3=1, N4=2, N5=3, and N6=0;

- N1=1, N2=0, N3=1, N4=2, N5=3, and N6=1;
N1=1, N2=0, N3=1, N4=2, N5=0, and N6=1;
N1=1, N2=0, N3=1, N4=3, N5=1, and N6=0;
N1=1, N2=0, N3=1, N4=3, N5=1, and N6=1;
5 N1=1, N2=0, N3=1, N4=3, N5=2, and N6=0;
N1=1, N2=0, N3=1, N4=3, N5=2, and N6=1;
N1=1, N2=0, N3=1, N4=3, N5=3, and N6=0;
N1=1, N2=0, N3=1, N4=3, N5=3, and N6=1;
N1=1, N2=0, N3=1, N4=3, N5=0, and N6=1;
10 N1=1, N2=0, N3=1, N4=1, N5=1, and N6=1;
N1=1, N2=0, N3=1, N4=1, N5=2, and N6=1;
N1=1, N2=0, N3=1, N4=1, N5=3, and N6=1;
N1=1, N2=1, N3=0, N4=1, N5=0, and N6=0;
N1=1, N2=1, N3=0, N4=2, N5=0, and N6=0;
15 N1=1, N2=1, N3=0, N4=3, N5=0, and N6=0;
N1=1, N2=1, N3=0, N4=1, N5=1, and N6=0;
N1=1, N2=1, N3=0, N4=1, N5=2, and N6=0;
N1=1, N2=1, N3=0, N4=1, N5=3, and N6=0;
N1=1, N2=1, N3=0, N4=1, N5=0, and N6=1;
20 N1=1, N2=1, N3=0, N4=2, N5=1, and N6=0;
N1=1, N2=1, N3=0, N4=2, N5=1, and N6=1;
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N1=1, N2=1, N3=0, N4=2, N5=2, and N6=1;
N1=1, N2=1, N3=0, N4=2, N5=3, and N6=0;

- N1=1, N2=1, N3=0, N4=2, N5=3, and N6=1;
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N1=1, N2=1, N3=0, N4=3, N5=1, and N6=1;
5 N1=1, N2=1, N3=0, N4=3, N5=2, and N6=0;
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N1=1, N2=1, N3=0, N4=3, N5=3, and N6=0;
N1=1, N2=1, N3=0, N4=3, N5=3, and N6=1;
N1=1, N2=1, N3=0, N4=3, N5=0, and N6=1;
10 N1=1, N2=1, N3=0, N4=1, N5=1, and N6=1;
N1=1, N2=1, N3=0, N4=1, N5=2, and N6=1;
N1=1, N2=1, N3=0, N4=1, N5=3, and N6=1;
N1=1, N2=1, N3=1, N4=1, N5=0, and N6=0;
N1=1, N2=1, N3=1, N4=2, N5=0, and N6=0;
15 N1=1, N2=1, N3=1, N4=3, N5=0, and N6=0;
N1=1, N2=1, N3=1, N4=1, N5=1, and N6=0;
N1=1, N2=1, N3=1, N4=1, N5=2, and N6=0;
N1=1, N2=1, N3=1, N4=1, N5=3, and N6=0;
N1=1, N2=1, N3=1, N4=1, N5=0, and N6=1;
20 N1=1, N2=1, N3=1, N4=2, N5=1, and N6=0;
N1=1, N2=1, N3=1, N4=2, N5=1, and N6=1;
N1=1, N2=1, N3=1, N4=2, N5=2, and N6=0;
N1=1, N2=1, N3=1, N4=2, N5=2, and N6=1;
N1=1, N2=1, N3=1, N4=2, N5=3, and N6=0;

- N1=1, N2=1, N3=1, N4=2, N5=3, and N6=1;
N1=1, N2=1, N3=1, N4=2, N5=0, and N6=1;
N1=1, N2=1, N3=1, N4=3, N5=1, and N6=0;
N1=1, N2=1, N3=1, N4=3, N5=1, and N6=1;
- 5 N1=1, N2=1, N3=1, N4=3, N5=2, and N6=0;
N1=1, N2=1, N3=1, N4=3, N5=2, and N6=1;
N1=1, N2=1, N3=1, N4=3, N5=3, and N6=0;
N1=1, N2=1, N3=1, N4=3, N5=3, and N6=1;
N1=1, N2=1, N3=1, N4=3, N5=0, and N6=1;
- 10 N1=1, N2=1, N3=1, N4=1, N5=1, and N6=1;
N1=1, N2=1, N3=1, N4=1, N5=2, and N6=1;
N1=1, N2=1, N3=1, N4=1, N5=3, and N6=1;
N1=1, N2=0, N3=0, N4=2, N5=1, and N6=0;
N1=1, N2=0, N3=0, N4=2, N5=2, and N6=0;
- 15 N1=1, N2=0, N3=0, N4=2, N5=3, and N6=0;
N1=1, N2=0, N3=0, N4=2, N5=0, and N6=1;
N1=1, N2=0, N3=0, N4=3, N5=1, and N6=0;
N1=1, N2=0, N3=0, N4=3, N5=2, and N6=0;
N1=1, N2=0, N3=0, N4=3, N5=3, and N6=0;
- 20 N1=1, N2=0, N3=0, N4=3, N5=0, and N6=1;
N1=1, N2=0, N3=0, N4=1, N5=2, and N6=1;
N1=1, N2=0, N3=0, N4=1, N5=3, and N6=1;
N1=1, N2=0, N3=0, N4=2, N5=1, and N6=1;
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- N1=1, N2=0, N3=0, N4=2, N5=3, and N6=1;
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N1=2, N2=0, N3=0, N4=1, N5=0, and N6=0;
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N1=2, N2=0, N3=0, N4=1, N5=2, and N6=0;
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20 N1=2, N2=0, N3=1, N4=2, N5=1, and N6=0;
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- N1=2, N2=0, N3=1, N4=2, N5=3, and N6=1;
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- 20 N1=2, N2=1, N3=0, N4=2, N5=1, and N6=0;
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N1=3, N2=0, N3=1, N4=3, N5=2, and N6=1;
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N1=3, N2=1, N3=0, N4=2, N5=0, and N6=0;
15 N1=3, N2=1, N3=0, N4=3, N5=0, and N6=0;
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N1=3, N2=1, N3=0, N4=1, N5=2, and N6=0;
N1=3, N2=1, N3=0, N4=1, N5=3, and N6=0;
N1=3, N2=1, N3=0, N4=1, N5=0, and N6=1;
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5 N1=3, N2=1, N3=0, N4=3, N5=2, and N6=0;
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N1=4, N2=1, N3=1, N4=1, N5=3, and N6=0;
N1=4, N2=1, N3=1, N4=1, N5=0, and N6=1;
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N1=4, N2=1, N3=1, N4=2, N5=1, and N6=1;
N1=4, N2=1, N3=1, N4=2, N5=2, and N6=0;
N1=4, N2=1, N3=1, N4=2, N5=2, and N6=1;
N1=4, N2=1, N3=1, N4=2, N5=3, and N6=0;

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N1=4, N2=1, N3=1, N4=2, N5=0, and N6=1;
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N1=4, N2=0, N3=0, N4=2, N5=0, and N6=1;
N1=4, N2=0, N3=0, N4=3, N5=1, and N6=0;
N1=4, N2=0, N3=0, N4=3, N5=2, and N6=0;
N1=4, N2=0, N3=0, N4=3, N5=3, and N6=0;
20 N1=4, N2=0, N3=0, N4=3, N5=0, and N6=1;
N1=4, N2=0, N3=0, N4=1, N5=2, and N6=1;
N1=4, N2=0, N3=0, N4=1, N5=3, and N6=1;
N1=4, N2=0, N3=0, N4=2, N5=1, and N6=1;
N1=4, N2=0, N3=0, N4=2, N5=2, and N6=1;

N1=4, N2=0, N3=0, N4=2, N5=3, and N6=1;

N1=4, N2=0, N3=0, N4=3, N5=1, and N6=1;

N1=4, N2=0, N3=0, N4=3, N5=2, and N6=1;

N1=4, N2=0, N3=0, N4=3, N5=3, and N6=1; or

5 N1=4, N2=0, N3=0, N4=1, N5=1, and N6=1;

13.) A compound ET; wherein E is comprised of one or more effector agents and wherein these effector agents have pharmacological activity referred to as "PA"; and wherein T is a targeting agent comprised of targeting ligands, or targeting
10 ligands and triggers; and wherein T increases the pharmacological activity PA to a target cell compared to nontarget cells;

and wherein a targeting ligand is a group that binds selectively to a structure associated with the target referred to as a "targeting receptor";
15 and wherein a trigger is a group that upon in vivo modification by biomolecules referred to as "triggering agents" becomes activated and modulates the activity of ET;

and wherein at the target cell there are present "m" different types of target
20 molecules designated as (p1...pm) at least one of which is present at increased amounts compared to at a nontarget cell, and wherein the type of the targeting molecule, which is increased on the target cell compared to a nontarget cell, may be different for a different nontarget cell;

and wherein ET can "interact with" the targeting molecules (p1...pm); wherein the term "interact with" means bind to a targeting receptor or have the trigger modified by a triggering agent.

5 wherein the number m is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 or about 20.

14.) A compound of claim 13 for which m is 2, 3, 4, 5 or about 6.

10 15.) An anticancer drug ET in which E comprises of one or more effector agents that evoke tumor cell killing and T comprises:

a) A group referred to as a "tumor selective targeting ligand" which selectively binds to a target receptor that is increased on the surface of the tumor cell or in the microenvironment of the tumor cell compared to that for a normal cell;

15 and

b) One or more of the following:

I. A tumor selective targeting ligand;

II. A group, referred to as a "masked intracellular transport ligand" which can be modified in vivo to give a group referred to as an "intracellular transport ligand" which binds to a tumor cell receptor that actively transports bound ligands into the tumor cell;

20

III. A group referred to as a "trigger" that can be modified in vivo, wherein in vivo modification activates the trigger and modulates the pharmacological activity PA;

IV. A group referred to as an "intracellular trapping ligand", which binds to one or more intracellular receptors or a group referred to as a "masked intracellular trapping ligand" which can be modified in vivo to give an "intracellular trapping ligand";

5

and wherein when a second targeting ligand is present in T then the first and second targeting ligands can bind simultaneously to two targeting receptor molecules;

10 and wherein when T consists of a targeting ligand and a trigger, and when in vivo modification of said trigger increases the tumor killing activity, the in vivo modification, which activates said trigger is caused by an enzyme or enzymatic activity that is increased at tumor cells or decreased at vital normal cells;

15 and wherein when T consists of a targeting ligand and a trigger, and when in vivo modification of said trigger decreases the tumor killing activity, the in vivo modification, which activates said trigger is caused by an enzyme or enzymatic activity that is decreased at tumor cells or increased at vital normal cells;
and provided that T is not an antibody, or an analog or component of an antibody,
20 or a complex of antibodies, or a bispecific antibody, or an analog of a bispecific antibody, or a natural protein, or a complex of natural proteins, or a protein, or a naturally occurring polymer, or a radiolabelled dimer, or a polymer to which is attached, at multiple sites, one or more cytotoxic drugs.

- 16.) A compound of claim 15 in which the effector agents is comprised of cytotoxic drugs, and/or radionuclides, and/or immunostimulatory drugs.
- 17.) A compound of claim 16 in which the effector agents are comprised of
5 cytotoxic drugs.
- 18.) A compound of claim 15 in which the effector agents are comprised of radionuclides.
- 10 19.) A compound of claim 15 in which the effector agents are cytotoxic drugs that produce synergistic cytotoxicity.
- 20.) A compound of claim 15 in which the effector agents stimulate the immune system.
- 15 21.) A compound of claim 15 in which the effector agents stimulate the innate immune system.
- 22.) A compound of claim 15 in which the effector agent is comprised of a group
20 that can irreversibly chemically modify one or more tumor components.
- 23.) A compound of claim 22 in which the effector agent irreversibly modifies a component that is present in increased amounts in tumor cells or in the microenvironment of tumor cells compared to normal cells or vital normal cells.

24.) A compound of claim 15 in which the effector agent comprises a drug that potentiates the cytotoxic activity of a second effector agent.

25.) A compound of claim 24 in which the effector agent comprises an inhibitor to
5 multidrug transporter proteins.

26.) A compound of claim 24 in which the effector comprises an inhibitor to a membrane transporter protein that facilitates uptake of a nutrient or biomolecule into tumor cells.

10

27.) A compound of claim 26 in which the effector comprises an inhibitor to nucleoside transporter proteins.

28.) An anticancer drug ET of claim 15 comprised of the following groups:

- 15 I. N1 targeting ligands, which may differ; and
- II. N2 masked intracellular transport ligands which may differ and
- III. N3 triggers, which may differ, designated "detoxification triggers" wherein activation of the trigger decreases the toxicity of the drug
- IV. N4 effector agents which may differ; and
- 20 V. N5 triggers which may differ, wherein activation of the trigger increases the toxicity of the drug; and
- VI. N6 intracellular trapping ligands or masked intracellular trapping ligands, which may differ;

and wherein:

N1 = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or about 10;

N2 = 0, 1, 2, 3, 4, 5 or about 5; N3 = 0, 1, 2, 3, 4, 5, or about 5;

N4 = 1, 2, 3, 4, 5, or about 5;

5 N5 = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or about 10;

N6 = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or about 10;

29.) A compound of claim 28 in which:

N1 = 1, 2, 3, or 4; N2 = 0, 1, or 2;

10 N3 = 0, 1, or 2; N4 = 1, 2, or 3;

N5 = 0, 1, 2, or 3; N6 = 1, 2, or 3;

30.) A compound of claim 29 wherein:

N1=1, N2=0, N3=1, N4=1, N5=0, and N6=0;

15 N1=1, N2=0, N3=0, N4=2, N5=0, and N6=0;

N1=1, N2=0, N3=0, N4=3, N5=0, and N6=0;

N1=1, N2=0, N3=0, N4=1, N5=1, and N6=0;

N1=1, N2=0, N3=0, N4=1, N5=2, and N6=0;

N1=1, N2=0, N3=0, N4=1, N5=3, and N6=0;

20 N1=1, N2=0, N3=0, N4=1, N5=0, and N6=1;

N1=1, N2=0, N3=1, N4=2, N5=0, and N6=0;

N1=1, N2=0, N3=1, N4=3, N5=0, and N6=0;

N1=1, N2=0, N3=1, N4=1, N5=1, and N6=0;

N1=1, N2=0, N3=1, N4=1, N5=2, and N6=0;

- N1=1, N2=0, N3=1, N4=1, N5=3, and N6=0;
N1=1, N2=0, N3=1, N4=1, N5=0, and N6=1;
N1=1, N2=0, N3=1, N4=2, N5=1, and N6=0;
N1=1, N2=0, N3=1, N4=2, N5=1, and N6=1;
5 N1=1, N2=0, N3=1, N4=2, N5=2, and N6=0;
N1=1, N2=0, N3=1, N4=2, N5=2, and N6=1;
N1=1, N2=0, N3=1, N4=2, N5=3, and N6=0;
N1=1, N2=0, N3=1, N4=2, N5=3, and N6=1;
N1=1, N2=0, N3=1, N4=2, N5=0, and N6=1;
10 N1=1, N2=0, N3=1, N4=3, N5=1, and N6=0;
N1=1, N2=0, N3=1, N4=3, N5=1, and N6=1;
N1=1, N2=0, N3=1, N4=3, N5=2, and N6=0;
N1=1, N2=0, N3=1, N4=3, N5=2, and N6=1;
N1=1, N2=0, N3=1, N4=3, N5=3, and N6=0;
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N1=1, N2=0, N3=1, N4=3, N5=0, and N6=1;
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N1=1, N2=0, N3=1, N4=1, N5=3, and N6=1;
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N1=1, N2=1, N3=0, N4=2, N5=0, and N6=0;
N1=1, N2=1, N3=0, N4=3, N5=0, and N6=0;
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- N1=1, N2=1, N3=0, N4=1, N5=3, and N6=0;
N1=1, N2=1, N3=0, N4=1, N5=0, and N6=1;
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N1=1, N2=1, N3=0, N4=2, N5=1, and N6=1;
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N1=1, N2=1, N3=0, N4=2, N5=2, and N6=1;
N1=1, N2=1, N3=0, N4=2, N5=3, and N6=0;
N1=1, N2=1, N3=0, N4=2, N5=3, and N6=1;
N1=1, N2=1, N3=0, N4=2, N5=0, and N6=1;
10 N1=1, N2=1, N3=0, N4=3, N5=1, and N6=0;
N1=1, N2=1, N3=0, N4=3, N5=1, and N6=1;
N1=1, N2=1, N3=0, N4=3, N5=2, and N6=0;
N1=1, N2=1, N3=0, N4=3, N5=2, and N6=1;
N1=1, N2=1, N3=0, N4=3, N5=3, and N6=0;
15 N1=1, N2=1, N3=0, N4=3, N5=3, and N6=1;
N1=1, N2=1, N3=0, N4=3, N5=0, and N6=1;
N1=1, N2=1, N3=0, N4=1, N5=1, and N6=1;
N1=1, N2=1, N3=0, N4=1, N5=2, and N6=1;
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- N1=4, N2=0, N3=1, N4=1, N5=3, and N6=0;
N1=4, N2=0, N3=1, N4=1, N5=0, and N6=1;
N1=4, N2=0, N3=1, N4=2, N5=1, and N6=0;
N1=4, N2=0, N3=1, N4=2, N5=1, and N6=1;
- 5 N1=4, N2=0, N3=1, N4=2, N5=2, and N6=0;
N1=4, N2=0, N3=1, N4=2, N5=2, and N6=1;
N1=4, N2=0, N3=1, N4=2, N5=3, and N6=0;
N1=4, N2=0, N3=1, N4=2, N5=3, and N6=1;
N1=4, N2=0, N3=1, N4=2, N5=0, and N6=1;
- 10 N1=4, N2=0, N3=1, N4=3, N5=1, and N6=0;
N1=4, N2=0, N3=1, N4=3, N5=1, and N6=1;
N1=4, N2=0, N3=1, N4=3, N5=2, and N6=0;
N1=4, N2=0, N3=1, N4=3, N5=2, and N6=1;
N1=4, N2=0, N3=1, N4=3, N5=3, and N6=0;
- 15 N1=4, N2=0, N3=1, N4=3, N5=3, and N6=1;
N1=4, N2=0, N3=1, N4=3, N5=0, and N6=1;
N1=4, N2=0, N3=1, N4=1, N5=1, and N6=1;
N1=4, N2=0, N3=1, N4=1, N5=2, and N6=1;
N1=4, N2=0, N3=1, N4=1, N5=3, and N6=1;
- 20 N1=4, N2=1, N3=0, N4=1, N5=0, and N6=0;
N1=4, N2=1, N3=0, N4=2, N5=0, and N6=0;
N1=4, N2=1, N3=0, N4=3, N5=0, and N6=0;
N1=4, N2=1, N3=0, N4=1, N5=1, and N6=0;
N1=4, N2=1, N3=0, N4=1, N5=2, and N6=0;

- N1=4, N2=1, N3=0, N4=1, N5=3, and N6=0;
N1=4, N2=1, N3=0, N4=1, N5=0, and N6=1;
N1=4, N2=1, N3=0, N4=2, N5=1, and N6=0;
N1=4, N2=1, N3=0, N4=2, N5=1, and N6=1;
5 N1=4, N2=1, N3=0, N4=2, N5=2, and N6=0;
N1=4, N2=1, N3=0, N4=2, N5=2, and N6=1;
N1=4, N2=1, N3=0, N4=2, N5=3, and N6=0;
N1=4, N2=1, N3=0, N4=2, N5=3, and N6=1;
N1=4, N2=1, N3=0, N4=2, N5=0, and N6=1;
10 N1=4, N2=1, N3=0, N4=3, N5=1, and N6=0;
N1=4, N2=1, N3=0, N4=3, N5=1, and N6=1;
N1=4, N2=1, N3=0, N4=3, N5=2, and N6=0;
N1=4, N2=1, N3=0, N4=3, N5=2, and N6=1;
N1=4, N2=1, N3=0, N4=3, N5=3, and N6=0;
15 N1=4, N2=1, N3=0, N4=3, N5=3, and N6=1;
N1=4, N2=1, N3=0, N4=3, N5=0, and N6=1;
N1=4, N2=1, N3=0, N4=1, N5=1, and N6=1;
N1=4, N2=1, N3=0, N4=1, N5=2, and N6=1;
N1=4, N2=1, N3=0, N4=1, N5=3, and N6=1;
20 N1=4, N2=1, N3=1, N4=1, N5=0, and N6=0;
N1=4, N2=1, N3=1, N4=2, N5=0, and N6=0;
N1=4, N2=1, N3=1, N4=3, N5=0, and N6=0;
N1=4, N2=1, N3=1, N4=1, N5=1, and N6=0;
N1=4, N2=1, N3=1, N4=1, N5=2, and N6=0;

- N1=4, N2=1, N3=1, N4=1, N5=3, and N6=0;
N1=4, N2=1, N3=1, N4=1, N5=0, and N6=1;
N1=4, N2=1, N3=1, N4=2, N5=1, and N6=0;
N1=4, N2=1, N3=1, N4=2, N5=1, and N6=1;
5 N1=4, N2=1, N3=1, N4=2, N5=2, and N6=0;
N1=4, N2=1, N3=1, N4=2, N5=2, and N6=1;
N1=4, N2=1, N3=1, N4=2, N5=3, and N6=0;
N1=4, N2=1, N3=1, N4=2, N5=3, and N6=1;
N1=4, N2=1, N3=1, N4=2, N5=0, and N6=1;
10 N1=4, N2=1, N3=1, N4=3, N5=1, and N6=0;
N1=4, N2=1, N3=1, N4=3, N5=1, and N6=1;
N1=4, N2=1, N3=1, N4=3, N5=2, and N6=0;
N1=4, N2=1, N3=1, N4=3, N5=2, and N6=1;
N1=4, N2=1, N3=1, N4=3, N5=3, and N6=0;
15 N1=4, N2=1, N3=1, N4=3, N5=3, and N6=1;
N1=4, N2=1, N3=1, N4=3, N5=0, and N6=1;
N1=4, N2=1, N3=1, N4=1, N5=1, and N6=1;
N1=4, N2=1, N3=1, N4=1, N5=2, and N6=1;
N1=4, N2=1, N3=1, N4=1, N5=3, and N6=1;
20 N1=4, N2=0, N3=0, N4=2, N5=1, and N6=0;
N1=4, N2=0, N3=0, N4=2, N5=2, and N6=0;
N1=4, N2=0, N3=0, N4=2, N5=3, and N6=0;
N1=4, N2=0, N3=0, N4=2, N5=0, and N6=1;
N1=4, N2=0, N3=0, N4=3, N5=1, and N6=0;

N1=4, N2=0, N3=0, N4=3, N5=2, and N6=0;

N1=4, N2=0, N3=0, N4=3, N5=3, and N6=0;

N1=4, N2=0, N3=0, N4=3, N5=0, and N6=1;

N1=4, N2=0, N3=0, N4=1, N5=2, and N6=1;

5 N1=4, N2=0, N3=0, N4=1, N5=3, and N6=1;

N1=4, N2=0, N3=0, N4=2, N5=1, and N6=1;

N1=4, N2=0, N3=0, N4=2, N5=2, and N6=1;

N1=4, N2=0, N3=0, N4=2, N5=3, and N6=1;

N1=4, N2=0, N3=0, N4=3, N5=1, and N6=1;

10 N1=4, N2=0, N3=0, N4=3, N5=2, and N6=1;

N1=4, N2=0, N3=0, N4=3, N5=3, and N6=1; or

N1=4, N2=0, N3=0, N4=1, N5=1, and N6=1;

31.) An anticancer drug of claim 30 in which the targeting ligands selectively bind to

15 target receptors on the surface of the tumor cell or in the microenvironment of the tumor cell, wherein the concentration of the target receptor is greater on the surface of the tumor cell or in the microenvironment of the tumor cell than on the surface or in the microenvironment of vital normal cells or normal cells.

20 32.) A compound of claim 31 with a trigger that increases cytotoxicity of the drug upon in vivo modification and wherein the in vivo modification, which activates the trigger is caused by an enzyme or enzymatic activity that is increased at tumor cells or decreased at vital normal cells or normal cells.

33.) A compound of claim 31 with a trigger that decreases the cytotoxicity of the drug upon in vivo modification and wherein the in vivo modification, which activates the trigger is caused by an enzyme or enzymatic activity that is decreased at tumor cells or increased at vital normal cells or normal cells.

5

34.) A compound of claim 30 in which the intracellular transport ligand binds to a molecule referred to as a "transporter molecule" to form a complex and wherein this complex binds to a target cell receptor that actively transports bound ligands into the tumor cell.

10

35.) A compound of claim 34 for which the concentration of transporter molecules is increased at the surface of tumor cells compared to vital normal cells or normal cells.

15

36.) A compound of claim 31, with two targeting ligands that selectively bind to target receptors on the surface of the tumor cell or in the microenvironment of the tumor cell, wherein the concentration of the target receptors is greater on the surface of the tumor cell or in the microenvironment of the tumor cell than on the surface or in the microenvironment of vital normal cells or normal cells.

20

37.) A compound of claim 36 in which the targeting ligands are different and bind to different types of targeting receptors.

38.) A compound of claim 31, with three targeting ligands that selectively bind to target receptors on the surface of the tumor cell or in the microenvironment of the tumor cell, wherein the concentration of the target receptors is greater on the surface of the tumor cell or in the microenvironment of the tumor cell than on the surface or in the microenvironment of vital normal cells or normal cells.

39.) A compound of claim 38 in which the targeting ligands are different and bind to different types of targeting receptors.

40.) Anticancer drug of claim 32 comprised of two or more targeting ligands, wherein at least one of the targeting ligands binds to a target receptor on the surface of the target cell or in the microenvironment of the target cell, wherein the target has an increased amount of that target receptor compared to a nontarget cell that binds to a second targeting ligand of the compound.

41.) A compound of claim 40 which comprises two different tumor selective targeting ligands and one effector agent and one trigger that increases the toxicity of the effector agent or where $N1=2$, and $N2=0$, and $N3=0$, and $N4=1$, and $N5=1$, and $N6=0$.

42.) A compound of claim 41 in which the effector agent is comprised of a cytotoxic drug.

43.) A compound of claim 41 in which the effector agent is comprised of a radionuclide.

44.) A compound of claim 41 in which the effector agent is comprised of a drug that
5 stimulates the immune system.

45.) A compound of claim 41 in which the effector agent is comprised of a group that can irreversibly chemically modify one or more tumor components.

10 46.) A compound of claim 41 in which the effector agent comprises an inhibitor to multidrug transporter proteins.

47.) A compound of claim 41 in which the effector agent comprises an inhibitor to nucleoside transporter proteins.

15

48.) A compound of claim 40, which comprises two different tumor selective targeting ligands, and one effector agent, and one trigger, and one masked intracellular transporter ligand, or where N1=2, and N2=1, and N3=0, and N4=1, and N5=1, and N6=0.

20

49.) A compound of claim 40, which comprises three different tumor selective targeting ligands and one effector agent, and one trigger that increases the toxicity of the effector agent, or where N1=3, and N2=0, and N3=0, and N4=1, and N5=1, and N6=0.

50.) A compound of claim 16 comprised of an anticancer drug with at least one targeting ligand that binds to a target receptor selected from the following list:

- 1) a cathepsin type protease
- 2) a collagenase
- 5 3) a gelatinase
- 4) a matrix metalloproteinase
- 5) a membrane type matrix metalloproteinase
- 6) alpha v beta 3 integrin
- 7) bombesin/gastrin releasing peptide receptors
- 10 8) cathepsin B
- 9) cathepsin D
- 10) cathepsin K
- 11) cathepsin L
- 12) cathepsin O
- 15 13) fibroblast activation protein
- 14) folate binding receptors
- 15) gastrin/cholecystokinin type B receptor
- 16) glutamate carboxypeptidase II or (PSMA)
- 17) guanidinobenzoatase
- 20 18) laminin receptor
- 19) matrilysin
- 20) matripase
- 21) melanocyte stimulating hormone receptor
- 22) nitrobenzylthioinosine-binding receptors

- 23) norepinephrine transporters
 - 24) nucleoside transporter proteins
 - 25) peripheral benzodiazepam binding receptors
 - 26) plasmin
 - 5 27) seprase
 - 28) sigma receptors
 - 29) somatostatin receptors
 - 30) stromelysin 3
 - 31) trypsin
 - 10 32) urokinase
 - 33) MMP 1
 - 34) MMP 2
 - 35) MMP 3
 - 36) MMP 7
 - 15 37) MMP 9
 - 38) Membrane type matrix metalloproteinase I
 - 39) MMP 12
 - 40) MMP 13
- 20 51.) An anticancer drug of claim 50 comprised of two targeting ligands for receptors that are increased on a tumor cell compared to a normal cell.
- 52.) A compound of claim 51 in which the targeting ligands are different and bind to different receptors.

53.) A compound of claim 16 in which ET is comprised of an anticancer drug with two targeting ligands that bind to target receptors selected from the following list:

- 1) a cathepsin type protease
- 2) a collagenase
- 5 3) a gelatinase
- 4) a matrix metalloproteinase
- 5) a membrane type matrix metalloproteinase
- 6) alpha v beta 3 integrin
- 7) bombesin/gastrin releasing peptide receptors
- 10 8) cathepsin B
- 9) cathepsin D
- 10) cathepsin K
- 11) cathepsin L
- 12) cathepsin O
- 15 13) fibroblast activation protein
- 14) folate binding receptors
- 15) gastrin/cholecystokinin type B receptor
- 16) glutamate carboxypeptidase II or (PSMA)
- 17) guanidinobenzoatase
- 20 18) laminin receptor
- 19) matrilysin
- 20) matripase
- 21) melanocyte stimulating hormone receptor
- 22) nitrobenzylthioinosine-binding receptors

- 23) norepinephrine transporters
- 24) nucleoside transporter proteins
- 25) peripheral benzodiazepam binding receptors
- 26) plasmin
- 5 27) seprase
- 28) sigma receptors
- 29) somatostatin receptors
- 30) stromelysin 3
- 31) trypsin
- 10 32) urokinase
- 33) MMP 1
- 34) MMP 2
- 35) MMP 3
- 36) MMP 7
- 15 37) MMP 9
- 38) Membrane type matrix metalloproteinase I
- 39) MMP 12
- 40) MMP 13

20 54.) A compound of claim 16 in which ET is comprised of an anticancer drug with three targeting ligands that bind to target receptors selected from the following list:

- 1) a cathepsin type protease
- 2) a collagenase
- 3) a gelatinase

- 4) a matrix metalloproteinase
- 5) a membrane type matrix metalloproteinase
- 6) alpha v beta 3 integrin
- 7) bombesin /gastrin releasing peptide receptors
- 5 8) cathepsin B
- 9) cathepsin D
- 10) cathepsin K
- 11) cathepsin L
- 12) cathepsin O
- 10 13) fibroblast activation protein
- 14) folate binding receptors
- 15) gastrin/cholecystokinin type B receptor
- 16) glutamate carboxypeptidase II or (PSMA)
- 17) guanidinobenzoatase
- 15 18) laminin receptor
- 19) matrilysin
- 20) matripase
- 21) melanocyte stimulating hormone receptor
- 22) nitrobenzylthioinosine-binding receptors
- 20 23) norepinephrine transporters
- 24) nucleoside transporter proteins
- 25) peripheral benzodiazepam binding receptors
- 26) plasmin
- 27) seprase

- 28) sigma receptors
 - 29) somatostatin receptors
 - 30) stromelysin 3
 - 31) trypsin
 - 5 32) urokinase
 - 33) MMP 1
 - 34) MMP 2
 - 35) MMP 3
 - 36) MMP 7
 - 10 37) MMP 9
 - 38) Membrane type matrix metalloproteinase I
 - 39) MMP 12
 - 40) MMP 13
- 15 55.) An anticancer drug of claim 16 comprised of one targeting ligand that binds the first target receptor (a1) and a second targeting ligand that binds to the second target receptor (a2) indicated in the pairs of (a1 — a2) listed below:
- urokinase — a cathepsin type protease; urokinase — a collagenase; urokinase — a gelatinase; urokinase — a matrix metalloproteinase; urokinase — a membrane
- 20 type matrix metalloproteinase; urokinase — alpha v beta 3 integrin; urokinase — bombesin/gastrin releasing peptide receptors; urokinase — cathepsin B;
- urokinase — cathepsin D; urokinase — to cathepsin K; urokinase — cathepsin L;
- urokinase — cathepsin O; urokinase — fibroblast activation protein; urokinase — folate binding receptors; urokinase — gastrin/cholecystokinin type B receptor;

- urokinase — glutamate carboxypeptidase II or (PSMA); urokinase —
 guanidinobenzoatase; urokinase — laminin receptor; urokinase — matrilysin;
 urokinase — matripase; urokinase — melanocyte stimulating hormone receptor;
 urokinase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 5 urokinase — norepinephrine transporters; urokinase — nucleoside transporter
 proteins; urokinase — peripheral benzodiazepam binding receptors; urokinase —
 plasmin; urokinase — seprase; urokinase — sigma receptors; urokinase —
 somatostatin receptors; urokinase — stromelysin 3; urokinase — trypsin;
 urokinase — urokinase; urokinase — MMP 1; urokinase — MMP 2; urokinase —
- 10 MMP 3; urokinase — MMP 7; urokinase — MMP 9; urokinase — membrane type
 matrix metalloproteinase I; urokinase — MMP 12; urokinase — MMP 13;
 urokinase — a tumor antigen; plasmin — a cathepsin type protease; plasmin —
 a collagenase; plasmin — a gelatinase; plasmin — a matrix metalloproteinase;
 plasmin — a membrane type matrix metalloproteinase; plasmin — alpha v beta 3
- 15 integrin; plasmin — bombesin /gastrin releasing peptide receptors; plasmin —
 cathepsin B; plasmin — cathepsin D; plasmin — to cathepsin K; plasmin —
 cathepsin L; plasmin — cathepsin O; plasmin — fibroblast activation protein;
 plasmin — folate binding receptors; plasmin — gastrin/cholecystokinin type B
 receptor; plasmin — glutamate carboxypeptidase II or (PSMA); plasmin —
- 20 guanidinobenzoatase; plasmin — laminin receptor; plasmin — matrilysin;
 plasmin — matripase; plasmin — melanocyte stimulating hormone receptor;
 plasmin — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
 plasmin — norepinephrine transporters; plasmin — nucleoside transporter

- proteins; plasmin — peripheral benzodiazepam binding receptors; plasmin — plasmin; plasmin — seprase; plasmin — sigma receptors; plasmin — somatostatin receptors; plasmin — stromelysin 3; plasmin — trypsin; plasmin — urokinase; plasmin — MMP 1; plasmin — MMP 2; plasmin —
- 5 MMP 3; plasmin — MMP 7; plasmin — MMP 9; plasmin — membrane type matrix metalloproteinase 1; plasmin — MMP 12; plasmin — MMP 13; plasmin — a tumor antigen; a collagenase — a cathepsin type protease; a collagenase — a collagenase; a collagenase — a gelatinase; a collagenase — a matrix metalloproteinase; a collagenase — a membrane type matrix metalloproteinase;
- 10 a collagenase — alpha v beta 3 integrin; a collagenase — bombesin /gastrin releasing peptide receptors; a collagenase — cathepsin B; a collagenase — cathepsin D; a collagenase — to cathepsin K; a collagenase — cathepsin L; a collagenase — cathepsin O; a collagenase — fibroblast activation protein; a collagenase — folate binding receptors; a collagenase — gastrin/cholecystokinin
- 15 type B receptor; a collagenase — glutamate carboxypeptidase II or (PSMA); a collagenase — guanidinobenzoate; a collagenase — laminin receptor; a collagenase — matrilysin; a collagenase — matripase; a collagenase — melanocyte stimulating hormone receptor; a collagenase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); a
- 20 collagenase — norepinephrine transporters; a collagenase — nucleoside transporter proteins; a collagenase — peripheral benzodiazepam binding receptors; a collagenase — seprase; a collagenase — sigma receptors; a collagenase — somatostatin receptors; a collagenase — stromelysin 3; a collagenase — trypsin; a collagenase — a collagenase; a collagenase — MMP 1;

a collagenase — MMP 2; a collagenase — MMP 3; a collagenase — MMP 7;
 a collagenase — MMP 9; a collagenase — membrane type matrix
 metalloproteinase I; a collagenase — MMP 12; a collagenase — MMP 13; a
 collagenase — a tumor antigen; a gelatinase — a cathepsin type protease; a
 5 gelatinase — a gelatinase; a gelatinase — a matrix metalloproteinase; a
 gelatinase — a membrane type matrix metalloproteinase; a gelatinase — alpha.v
 beta 3 integrin; a gelatinase — bombesin /gastrin releasing peptide receptors; a
 gelatinase — cathepsin B; a gelatinase — cathepsin D; a gelatinase — to,
 cathepsin K; a gelatinase — cathepsin L; a gelatinase — cathepsin O; a
 10 gelatinase — fibroblast activation protein; a gelatinase — folate binding
 receptors; a gelatinase — gastrin/cholecystokinin type B receptor; a gelatinase
 — glutamate carboxypeptidase II or (PSMA); a gelatinase —
 guanidinobenzoatase; a gelatinase — laminin receptor; a gelatinase —
 matrilysin; a gelatinase — matrilysin; a gelatinase — melanocyte stimulating
 15 hormone receptor; a gelatinase — nitrobenzylthioinosine-binding receptors or
 (nucleoside transporter); a gelatinase — norepinephrine transporters; a
 gelatinase — nucleoside transporter proteins; a gelatinase — peripheral
 benzodiazepam binding receptors; a gelatinase — seprase; a gelatinase —
 sigma receptors; a gelatinase — somatostatin receptors; a gelatinase —
 20 stromelysin 3; a gelatinase — trypsin; a gelatinase — MMP 1;
 a gelatinase — MMP 2; a gelatinase — MMP 3; a gelatinase — MMP 7; a
 gelatinase — MMP 9; a gelatinase — membrane type matrix metalloproteinase I;
 a gelatinase — MMP 12; a gelatinase — MMP 13; a gelatinase — a tumor
 antigen; a matrix metalloproteinase — a cathepsin type protease; a matrix

metalloproteinase — a collagenase; a matrix metalloproteinase — a gelatinase;
a matrix metalloproteinase — a matrix metalloproteinase; a matrix
metalloproteinase — a membrane type matrix metalloproteinase; a matrix
metalloproteinase — alpha v beta 3 integrin; a matrix metalloproteinase —
5 bombesin/gastrin releasing peptide receptors; a matrix metalloproteinase —
cathepsin B; a matrix metalloproteinase — cathepsin D; a matrix
metalloproteinase — to cathepsin K; a matrix metalloproteinase — cathepsin L;
a matrix metalloproteinase — cathepsin O; a matrix metalloproteinase —
fibroblast activation protein; a matrix metalloproteinase — folate binding
10 receptors; a matrix metalloproteinase — gastrin/cholecystokinin type B receptor;
a matrix metalloproteinase — glutamate carboxypeptidase II or (PSMA); a matrix
metalloproteinase — guanidinobenzoate; a matrix metalloproteinase — laminin
receptor; a matrix metalloproteinase — matrilysin; a matrix metalloproteinase —
matrilysin; a matrix metalloproteinase — melanocyte stimulating hormone
15 receptor; a matrix metalloproteinase — nitrobenzylthioinosine-binding receptors
or (nucleoside transporter); a matrix metalloproteinase — norepinephrine
transporters; a matrix metalloproteinase — nucleoside transporter proteins; a
matrix metalloproteinase — peripheral benzodiazepam binding receptors; a matrix
metalloproteinase — plasmin; a matrix metalloproteinase — seprase; a matrix
20 metalloproteinase — sigma receptors; a matrix metalloproteinase — somatostatin
receptors; a matrix metalloproteinase — stromelysin 3; a matrix
metalloproteinase — trypsin; a matrix metalloproteinase — a matrix
metalloproteinase; a matrix metalloproteinase — MMP 1; a matrix
metalloproteinase — MMP 2; a matrix metalloproteinase — MMP 3; a matrix

- metalloproteinase — MMP 7; a matrix metalloproteinase — MMP 9; a matrix metalloproteinase — membrane type matrix metalloproteinase I; a matrix metalloproteinase — MMP 12; a matrix metalloproteinase — MMP 13; a matrix metalloproteinase — a tumor antigen; a membrane type metalloproteinase —
- 5 a cathepsin type protease; a membrane type metalloproteinase — a membrane type matrix metalloproteinase; a membrane type metalloproteinase — alpha v beta 3 integrin; a membrane type metalloproteinase — bombesin /gastrin releasing peptide receptors; a membrane type metalloproteinase — cathepsin B; a membrane type metalloproteinase — cathepsin D; a membrane type
- 10 metalloproteinase — to cathepsin K; a membrane type metalloproteinase — cathepsin L; a membrane type metalloproteinase — cathepsin O; a membrane type metalloproteinase — fibroblast activation protein; a membrane type metalloproteinase — folate binding receptors; a membrane type metalloproteinase — gastrin/cholecystokinin type B receptor; a membrane type
- 15 metalloproteinase — glutamate carboxypeptidase II or (PSMA); a membrane type metalloproteinase — guanidinobenzoate; a membrane type metalloproteinase — laminin receptor; a membrane type metalloproteinase — matrilysin; a membrane type metalloproteinase — matripase; a membrane type metalloproteinase — melanocyte stimulating hormone receptor;
- 20 a membrane type metalloproteinase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); a membrane type metalloproteinase — norepinephrine transporters; a membrane type metalloproteinase — nucleoside transporter proteins; a membrane type metalloproteinase — peripheral benzodiazepam binding receptors; a membrane type metalloproteinase — seprase; a membrane type

metalloproteinase — sigma receptors; a membrane type metalloproteinase —
 somatostatin receptors; a membrane type metalloproteinase — stromelysin 3; a
 membrane type metalloproteinase — trypsin; a membrane type metalloproteinase
 — MMP 1; a membrane type metalloproteinase — MMP 2; a membrane type
 5 metalloproteinase — MMP 3; a membrane type metalloproteinase — MMP 7; a
 membrane type metalloproteinase — MMP 9; a membrane type
 metalloproteinase — membrane type matrix metalloproteinase I; a membrane type
 metalloproteinase — MMP 12; a membrane type metalloproteinase — MMP 13;
 a membrane type metalloproteinase — a tumor antigen; alpha v beta 3 integrin — a
 10 cathepsin type protease; alpha v beta 3 integrin — alpha v beta 3 integrin;
 alpha v beta 3 integrin — bombesin /gastrin releasing peptide receptors; alpha v
 beta 3 integrin — cathepsin B; alpha v beta 3 integrin — cathepsin D; alpha v
 beta 3 integrin — cathepsin K; alpha v beta 3 integrin — cathepsin L; alpha v
 beta 3 integrin — cathepsin O; alpha v beta 3 integrin — fibroblast activation
 15 protein; alpha v beta 3 integrin — folate binding receptors; alpha v beta 3
 integrin — gastrin/cholecystokinin type B receptor; alpha v beta 3 integrin —
 glutamate carboxypeptidase II or (PSMA); alpha v beta 3 integrin —
 guanidinobenzoatase; alpha v beta 3 integrin — laminin receptor; alpha v beta
 3 integrin — matrilysin; alpha v beta 3 integrin — matripase; alpha v beta 3
 20 integrin — melanocyte stimulating hormone receptor; alpha v beta 3 integrin —
 nitrobenzylthioinosine-binding receptors or (nucleoside transporter); alpha v beta
 3 integrin — norepinephrine transporters; alpha v beta 3 integrin — nucleoside
 transporter proteins; alpha v beta 3 integrin — peripheral benzodiazepam binding
 receptors; alpha v beta 3 integrin — seprase;

alpha v beta 3 integrin — sigma receptors; alpha v beta 3 integrin — somatostatin
 receptors; alpha v beta 3 integrin — stromelysin 3; alpha v beta 3 integrin —
 trypsin; alpha v beta 3 integrin — MMP 1; alpha v beta 3 integrin — MMP 2;
 alpha v beta 3 integrin — MMP 3; alpha v beta 3 integrin — MMP 7; alpha v
 5 beta 3 integrin — MMP 9; alpha v beta 3 integrin — membrane type matrix
 metalloproteinase I; alpha v beta 3 integrin — MMP 12; alpha v beta 3 integrin —
 MMP 13; alpha v beta 3 integrin — a tumor antigen; cathepsin B — a cathepsin
 type protease; cathepsin B — bombesin /gastrin releasing peptide receptors;
 cathepsin B — cathepsin B; cathepsin B — cathepsin D; cathepsin B — to
 10 cathepsin K; cathepsin B — cathepsin L; cathepsin B — cathepsin O;
 cathepsin B — fibroblast activation protein; cathepsin B — folate binding
 receptors; cathepsin B — gastrin/cholecystokinin type B receptor; cathepsin B —
 glutamate carboxypeptidase II or (PSMA); cathepsin B — guanidinobenzoate;
 cathepsin B — laminin receptor; cathepsin B — matrilysin; cathepsin B —
 15 matrilysin; cathepsin B — melanocyte stimulating hormone receptor; cathepsin
 B — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
 cathepsin B — norepinephrine transporters; cathepsin B — nucleoside
 transporter proteins; cathepsin B — peripheral benzodiazepam binding receptors;
 cathepsin B — seprase; cathepsin B — sigma receptors; cathepsin B —
 20 somatostatin receptors; cathepsin B — stromelysin 3; cathepsin B — trypsin;
 cathepsin B — MMP 1; cathepsin B — MMP 2; cathepsin B — MMP 3;
 cathepsin B — MMP 7; cathepsin B — MMP 9; cathepsin B — membrane type
 matrix metalloproteinase I; cathepsin B — MMP 12; cathepsin B — MMP 13;
 cathepsin B — a tumor antigen; bombesin/ gastrin releasing peptide receptors — a

- cathepsin type protease; bombesin/ gastrin releasing peptide receptors —
bombesin /gastrin releasing peptide receptors; bombesin/ gastrin releasing
peptide receptors — cathepsin B; bombesin/ gastrin releasing peptide receptors -
— cathepsin D; bombesin/ gastrin releasing peptide receptors — to cathepsin K;
5 bombesin/ gastrin releasing peptide receptors — cathepsin L; bombesin/ gastrin
releasing peptide receptors — cathepsin O; bombesin/ gastrin releasing peptide
receptors — fibroblast activation protein; bombesin/ gastrin releasing peptide
receptors — folate binding receptors; bombesin/ gastrin releasing peptide
receptors — gastrin/cholecystokinin type B receptor; bombesin/ gastrin releasing
10 peptide receptors — glutamate carboxypeptidase II or (PSMA); bombesin/ gastrin
releasing peptide receptors — guanidinobenzoate; bombesin/ gastrin releasing
peptide receptors — laminin receptor; bombesin/ gastrin releasing peptide
receptors — matrilysin; bombesin/ gastrin releasing peptide receptors —
matrilysin; bombesin/ gastrin releasing peptide receptors — melanocyte
15 stimulating hormone receptor; bombesin/ gastrin releasing peptide receptors —
nitrobenzylthioinosine-binding receptors or (nucleoside transporter); bombesin/
gastrin releasing peptide receptors — norepinephrine transporters; bombesin/
gastrin releasing peptide receptors — nucleoside transporter proteins; bombesin/
gastrin releasing peptide receptors — peripheral benzodiazepam binding receptors;
20 bombesin/ gastrin releasing peptide receptors — seprase; bombesin/ gastrin
releasing peptide receptors — sigma receptors; bombesin/ gastrin releasing
peptide receptors — somatostatin receptors; bombesin/ gastrin releasing peptide
receptors — stromelysin 3; bombesin/ gastrin releasing peptide receptors —
trypsin; bombesin/ gastrin releasing peptide receptors — MMP 1; bombesin/

- gastrin releasing peptide receptors — MMP 2; bombesin/ gastrin releasing peptide receptors — MMP 3; bombesin/ gastrin releasing peptide receptors — MMP 7; bombesin/ gastrin releasing peptide receptors — MMP 9; bombesin/ gastrin releasing peptide receptors — membrane type matrix metalloproteinase I; bombesin/ gastrin releasing peptide receptors — MMP 12; bombesin/ gastrin releasing peptide receptors — MMP 13; bombesin/ gastrin releasing peptide receptors — a tumor antigen; fibroblast activation protein — a cathepsin type protease; fibroblast activation protein — cathepsin D; fibroblast activation protein — to cathepsin K; fibroblast activation protein — cathepsin L; fibroblast activation protein — cathepsin O; fibroblast activation protein — fibroblast activation protein; fibroblast activation protein — folate binding receptors; fibroblast activation protein — gastrin/cholecystokinin type B receptor; fibroblast activation protein — glutamate carboxypeptidase II or (PSMA); fibroblast activation protein — guanidinobenzoate; fibroblast activation protein — laminin receptor; fibroblast activation protein — matrilysin; fibroblast activation protein — matrilysin; fibroblast activation protein — melanocyte stimulating hormone receptor; fibroblast activation protein — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); fibroblast activation protein — norepinephrine transporters; fibroblast activation protein — nucleoside transporter proteins; fibroblast activation protein — peripheral benzodiazepam binding receptors; fibroblast activation protein — plasmin; fibroblast activation protein — seprase; fibroblast activation protein — sigma receptors; fibroblast activation protein — somatostatin receptors; fibroblast activation protein — stromelysin 3; fibroblast activation protein — trypsin; fibroblast activation protein — MMP 1; fibroblast

- activation protein — MMP 2; fibroblast activation protein — MMP 3; fibroblast activation protein — MMP 7; fibroblast activation protein — MMP 9; fibroblast activation protein — membrane type matrix metalloproteinase I; fibroblast activation protein — MMP 12; fibroblast activation protein — MMP 13; fibroblast
- 5 activation protein — a tumor antigen; glutamate carboxypeptidase II or PSMA — cathepsin D; glutamate carboxypeptidase II or PSMA — to cathepsin K; glutamate carboxypeptidase II or PSMA — cathepsin L; glutamate carboxypeptidase II or PSMA — cathepsin O; glutamate carboxypeptidase II or PSMA — fibroblast activation protein; glutamate carboxypeptidase II or PSMA —
- 10 folate binding receptors; glutamate carboxypeptidase II or PSMA — gastrin/cholecystokinin type B receptor; glutamate carboxypeptidase II or PSMA — glutamate carboxypeptidase II or (PSMA); glutamate carboxypeptidase II or PSMA — guanidinobenzoate; glutamate carboxypeptidase II or PSMA — laminin receptor; glutamate carboxypeptidase II or PSMA — matrilysin;
- 15 glutamate carboxypeptidase II or PSMA — matrilysin; glutamate carboxypeptidase II or PSMA — melanocyte stimulating hormone receptor; glutamate carboxypeptidase II or PSMA — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); glutamate carboxypeptidase II or PSMA — nucleoside transporter proteins; glutamate carboxypeptidase II or PSMA — peripheral
- 20 benzodiazepam binding receptors; glutamate carboxypeptidase II or PSMA — seprase; glutamate carboxypeptidase II or PSMA — sigma receptors; glutamate carboxypeptidase II or PSMA — somatostatin receptors; glutamate carboxypeptidase II or PSMA — stromelysin 3; glutamate carboxypeptidase II or PSMA — trypsin; glutamate carboxypeptidase II or PSMA — MMP 1; glutamate

- carboxypeptidase II or PSMA — MMP 2; glutamate carboxypeptidase II or PSMA — MMP 3; glutamate carboxypeptidase II or PSMA — MMP 7; glutamate carboxypeptidase II or PSMA — MMP 9; glutamate carboxypeptidase II or PSMA — membrane type matrix metalloproteinase I; glutamate carboxypeptidase II or PSMA — MMP 12; glutamate carboxypeptidase II or PSMA — MMP 13; glutamate carboxypeptidase II or PSMA — a tumor antigen; laminin receptor — a cathepsin type protease; laminin receptor — cathepsin B; laminin receptor — cathepsin D; laminin receptor — to cathepsin K; laminin receptor — cathepsin L; laminin receptor — cathepsin O; laminin receptor — fibroblast activation protein; laminin receptor — folate binding receptors; laminin receptor — gastrin/cholecystokinin type B receptor; laminin receptor — guanidinobenzoate; laminin receptor — laminin receptor; laminin receptor — matrilysin; laminin receptor — matrilysin; laminin receptor — melanocyte stimulating hormone receptor; laminin receptor — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); laminin receptor — norepinephrine transporters; laminin receptor — nucleoside transporter proteins; laminin receptor — peripheral benzodiazepam binding receptors; laminin receptor — seprase; laminin receptor — sigma receptors; laminin receptor — somatostatin receptors; laminin receptor — stromelysin 3; laminin receptor — trypsin; laminin receptor — MMP 1; laminin receptor — MMP 2; laminin receptor — MMP 3; laminin receptor — MMP 7; laminin receptor — MMP 9; laminin receptor — membrane type matrix metalloproteinase I; laminin receptor — MMP 12; laminin receptor — MMP 13; laminin receptor — a tumor antigen; seprase — a cathepsin type protease; seprase — cathepsin D; seprase — to cathepsin K; seprase — cathepsin L;

seprase — cathepsin O; seprase — fibroblast activation protein; seprase — folate binding receptors; seprase — gastrin/cholecystokinin type B receptor; seprase — guanidinobenzoatase; seprase — matripase; seprase — melanocyte stimulating hormone receptor; seprase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); seprase — norepinephrine transporters; seprase — nucleoside transporter proteins; seprase — peripheral benzodiazepam binding receptors; seprase — seprase; seprase — sigma receptors; seprase — somatostatin receptors; seprase — stromelysin 3; seprase — trypsin; seprase — MMP 1; seprase — MMP 2; seprase — MMP 3; seprase — MMP 7; seprase — MMP 9; seprase — membrane type matrix metalloproteinase I; seprase — MMP 12; seprase — MMP 13; seprase — a tumor antigen; guanidinobenzoatase — a cathepsin type protease; guanidinobenzoatase — cathepsin D; guanidinobenzoatase — cathepsin K; guanidinobenzoatase — cathepsin L; guanidinobenzoatase — cathepsin O; guanidinobenzoatase — fibroblast activation protein; guanidinobenzoatase — folate binding receptors; guanidinobenzoatase — gastrin/cholecystokinin type B receptor; guanidinobenzoatase — guanidinobenzoatase; guanidinobenzoatase — matripase; guanidinobenzoatase — melanocyte stimulating hormone receptor; guanidinobenzoatase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); guanidinobenzoatase — norepinephrine transporters; guanidinobenzoatase — nucleoside transporter proteins; guanidinobenzoatase — peripheral benzodiazepam binding receptors; guanidinobenzoatase — sigma receptors; guanidinobenzoatase — somatostatin receptors; guanidinobenzoatase — stromelysin 3; guanidinobenzoatase — trypsin;

- guanidinobenzoatase — MMP 1; guanidinobenzoatase — MMP 2;
guanidinobenzoatase — MMP 3; guanidinobenzoatase — MMP 7;
guanidinobenzoatase — MMP 9; guanidinobenzoatase — membrane type matrix
metalloproteinase I; guanidinobenzoatase — MMP 12; guanidinobenzoatase —
5 MMP 13; guanidinobenzoatase — a tumor antigen; peripheral benzodiazepam
binding receptors — a cathepsin type protease; peripheral benzodiazepam
binding receptors — cathepsin D; peripheral benzodiazepam binding receptors —
to cathepsin K; peripheral benzodiazepam binding receptors — cathepsin L;
peripheral benzodiazepam binding receptors — cathepsin O; peripheral
10 benzodiazepam binding receptors — fibroblast activation protein; peripheral
benzodiazepam binding receptors — folate binding receptors; peripheral
benzodiazepam binding receptors — gastrin/cholecystokinin type B receptor;
peripheral benzodiazepam binding receptors — guanidinobenzoatase; peripheral
benzodiazepam binding receptors — matipase; peripheral benzodiazepam
15 binding receptors — melanocyte stimulating hormone receptor; peripheral
benzodiazepam binding receptors — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter); peripheral benzodiazepam binding receptors —
norepinephrine transporters; peripheral benzodiazepam binding receptors —
nucleoside transporter proteins; peripheral benzodiazepam binding receptors —
20 peripheral benzodiazepam binding receptors; peripheral benzodiazepam binding
receptors — sigma receptors; peripheral benzodiazepam binding receptors —
somatostatin receptors; peripheral benzodiazepam binding receptors —
stromelysin 3; peripheral benzodiazepam binding receptors — trypsin;
peripheral benzodiazepam binding receptors — MMP 1; peripheral

- benzodiazepam binding receptors — MMP 2; peripheral benzodiazepam binding receptors — MMP 3; peripheral benzodiazepam binding receptors — MMP 7; peripheral benzodiazepam binding receptors — MMP 9; peripheral benzodiazepam binding receptors — membrane type matrix metalloproteinase I;
- 5 peripheral benzodiazepam binding receptors — MMP 12; peripheral benzodiazepam binding receptors — MMP 13; peripheral benzodiazepam binding receptors — a tumor antigen; folate binding receptors — a cathepsin type protease; folate binding receptors — cathepsin D; folate binding receptors — to cathepsin K; folate binding receptors — cathepsin L; folate binding receptors — cathepsin
- 10 O; folate binding receptors — fibroblast activation protein; folate binding receptors — folate binding receptors; folate binding receptors — matrilysin; folate binding receptors — melanocyte stimulating hormone receptor; folate binding receptors — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); folate binding receptors — norepinephrine transporters; folate
- 15 binding receptors — nucleoside transporter proteins; folate binding receptors — sigma receptors; folate binding receptors — somatostatin receptors; folate binding receptors — stromelysin 3; folate binding receptors — trypsin; folate binding receptors — MMP 1; folate binding receptors — MMP 2; folate binding receptors — MMP 3; folate binding receptors — MMP 7; folate binding
- 20 receptors — MMP 9; folate binding receptors — membrane type matrix metalloproteinase I; folate binding receptors — MMP 12; folate binding receptors — MMP 13; folate binding receptors — a tumor antigen; folate binding receptors — a cathepsin type protease; folate binding receptors — cathepsin D;

folate binding receptors — to cathepsin K; folate binding receptors — cathepsin L; folate binding receptors — cathepsin O; folate binding receptors — fibroblast activation protein; folate binding receptors — folate binding receptors; folate binding receptors — matrilysin; folate binding receptors — melanocyte stimulating hormone receptor; folate binding receptors — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); folate binding receptors — norepinephrine transporters; folate binding receptors — nucleoside transporter proteins; folate binding receptors — sigma receptors; folate binding receptors — somatostatin receptors; folate binding receptors — stromelysin 3; folate binding receptors — trypsin; folate binding receptors — MMP 1; folate binding receptors — MMP 2; folate binding receptors — MMP 3; folate binding receptors — MMP 7; folate binding receptors — MMP 9; folate binding receptors — membrane type matrix metalloproteinase 1; folate binding receptors — MMP 12; folate binding receptors — MMP 13; folate binding receptors — a tumor antigen; nucleoside transporter proteins — a cathepsin type protease; nucleoside transporter proteins — cathepsin D; nucleoside transporter proteins — to cathepsin K; nucleoside transporter proteins — cathepsin L; nucleoside transporter proteins — cathepsin O; nucleoside transporter proteins — fibroblast activation protein; nucleoside transporter proteins — nucleoside transporter proteins; nucleoside transporter proteins — matrilysin; nucleoside transporter proteins — melanocyte stimulating hormone receptor; nucleoside transporter proteins — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); nucleoside transporter proteins — norepinephrine transporters; nucleoside transporter proteins — nucleoside transporter proteins; nucleoside transporter

- proteins — sigma receptors; nucleoside transporter proteins — somatostatin receptors; nucleoside transporter proteins — stromelysin 3; nucleoside transporter proteins — trypsin; nucleoside transporter proteins — MMP 1; nucleoside transporter proteins — MMP 2; nucleoside transporter proteins —
- 5 MMP 3; nucleoside transporter proteins — MMP 7; nucleoside transporter proteins — MMP 9; nucleoside transporter proteins — membrane type matrix metalloproteinase I; nucleoside transporter proteins — MMP 12; nucleoside transporter proteins — MMP 13; nucleoside transporter proteins — a tumor antigen; melanocyte stimulating hormone receptor — a cathepsin type protease;
- 10 melanocyte stimulating hormone receptor — cathepsin D; melanocyte stimulating hormone receptor — cathepsin K; melanocyte stimulating hormone receptor — cathepsin L; melanocyte stimulating hormone receptor — cathepsin O; melanocyte stimulating hormone receptor — fibroblast activation protein; melanocyte stimulating hormone receptor — melanocyte stimulating hormone
- 15 receptor; melanocyte stimulating hormone receptor — melanocyte stimulating hormone receptor; melanocyte stimulating hormone receptor — nitrobenzylthioinosine-binding receptors or (nucleoside transporter); melanocyte stimulating hormone receptor — norepinephrine transporters; melanocyte stimulating hormone receptor — nucleoside transporter proteins; melanocyte
- 20 stimulating hormone receptor — sigma receptors; melanocyte stimulating hormone receptor — somatostatin receptors; melanocyte stimulating hormone receptor — stromelysin 3; melanocyte stimulating hormone receptor — trypsin; melanocyte stimulating hormone receptor — MMP 1; melanocyte stimulating hormone receptor — MMP 2; melanocyte stimulating hormone receptor — MMP 3;

- melanocyte stimulating hormone receptor — MMP 7; melanocyte stimulating hormone receptor — MMP 9; melanocyte stimulating hormone receptor — membrane type matrix metalloproteinase I; melanocyte stimulating hormone receptor — MMP 12; melanocyte stimulating hormone receptor — MMP 13;
- 5 melanocyte stimulating hormone receptor — a tumor antigen; sigma receptors — a cathepsin type protease; sigma receptors — cathepsin D; sigma receptors — cathepsin K; sigma receptors — cathepsin L; sigma receptors — cathepsin O; sigma receptors — fibroblast activation protein; sigma receptors — sigma receptors; sigma receptors — matipase; sigma receptors — norepinephrine
- 10 transporters; sigma receptors — sigma receptors; sigma receptors — somatostatin receptors; sigma receptors — stromelysin 3; sigma receptors — trypsin; sigma receptors — MMP 1; sigma receptors — MMP 2; sigma receptors — MMP 3; sigma receptors — MMP 7; sigma receptors — MMP 9; sigma receptors — membrane type matrix metalloproteinase I; sigma receptors —
- 15 MMP 12; sigma receptors — MMP 13; sigma receptors — a tumor antigen; somatostatin receptors — a cathepsin type protease; somatostatin receptors — cathepsin D; somatostatin receptors — cathepsin K; somatostatin receptors — cathepsin L; somatostatin receptors — cathepsin O; somatostatin receptors — fibroblast activation protein; somatostatin receptors — somatostatin receptors;
- 20 somatostatin receptors — matipase; somatostatin receptors — melanocyte stimulating hormone receptor; somatostatin receptors — sigma receptors; somatostatin receptors — somatostatin receptors; somatostatin receptors — stromelysin 3; somatostatin receptors — trypsin; somatostatin receptors — MMP 1; somatostatin receptors — MMP 2; somatostatin receptors — MMP 3;

- somatostatin receptors — MMP 7; somatostatin receptors — MMP 9;
 somatostatin receptors — membrane type matrix metalloproteinase I; somatostatin
 receptors — MMP 12; somatostatin receptors — MMP 13; somatostatin
 receptors — a tumor antigen; stromelysin 3 — a cathepsin type protease;
- 5 stromelysin 3 — cathepsin D; stromelysin 3 — to cathepsin K; stromelysin 3 —
 cathepsin L; stromelysin 3 — cathepsin O; stromelysin 3 — fibroblast activation
 protein; stromelysin 3 — stromelysin 3; stromelysin 3 — matipase;
 stromelysin 3 — melanocyte stimulating hormone receptor; stromelysin 3 —
 somatostatin receptors; stromelysin 3 — trypsin; stromelysin 3 — MMP 1;
- 10 stromelysin 3 — MMP 2; stromelysin 3 — MMP 3; stromelysin 3 — MMP 7;
 stromelysin 3 — MMP 9; stromelysin 3 — membrane type matrix
 metalloproteinase I; stromelysin 3 — MMP 12; stromelysin 3 — MMP 13;
 stromelysin 3 — a tumor antigen; trypsin — a cathepsin type protease; trypsin —
 cathepsin D; trypsin — to cathepsin K; trypsin — cathepsin L; trypsin —
- 15 cathepsin O; trypsin — fibroblast activation protein; trypsin — trypsin; trypsin —
 matipase; trypsin — melanocyte stimulating hormone receptor; trypsin —
 stromelysin 3; trypsin — MMP 1; trypsin — MMP 2; trypsin — MMP 3;
 trypsin — MMP 7; trypsin — MMP 9; trypsin — membrane type matrix
 metalloproteinase I; trypsin — MMP 12; trypsin — MMP 13; trypsin — a tumor
- 20 antigen; MMP 1 — a cathepsin type protease; MMP 1 — cathepsin D; MMP 1
 — to cathepsin K; MMP 1 — cathepsin L; MMP 1 — cathepsin O; MMP 1 —
 fibroblast activation protein; MMP 1 — matipase; MMP 1 — melanocyte
 stimulating hormone receptor; MMP 1 — stromelysin 3; MMP 1 — MMP 1;
 MMP 1 — MMP 2; MMP 1 — MMP 3; MMP 1 — MMP 7; MMP 1 — MMP 9;

MMP 1 — membrane type matrix metalloproteinase I; MMP 1 — MMP 12; MMP
 1 — MMP 13; MMP 1 — a tumor antigen; MMP-2 —
 a cathepsin type protease; MMP-2 — cathepsin D; MMP-2 — to cathepsin K;
 MMP-2 — cathepsin L; MMP-2 — cathepsin O; MMP-2 — fibroblast activation
 5 protein; MMP-2 — matipase; MMP-2 — melanocyte stimulating hormone
 receptor; MMP-2 — stromelysin 3; MMP-2 — MMP 2; MMP-2 — MMP 3;
 MMP-2 — MMP 7; MMP-2 — MMP 9; MMP-2 — membrane type matrix
 metalloproteinase I; MMP-2 — MMP-2; MMP-2 — MMP-3; MMP-2 — a tumor
 antigen; MMP-3 — a cathepsin type protease; MMP-3 — cathepsin D; MMP-3 -
 10 — to cathepsin K; MMP-3 — cathepsin L; MMP-3 — cathepsin O; MMP-3 —
 matipase; MMP-3 — MMP 3; MMP-3 — MMP 7; MMP-3 — MMP 9; MMP-3 -
 — membrane type matrix metalloproteinase I; MMP-3 — MMP-3; MMP-3 — a
 tumor antigen; MMP 7 — a cathepsin type protease; MMP 7 — cathepsin D;
 MMP 7 — to cathepsin K; MMP 7 — cathepsin L; MMP 7 — cathepsin O;
 15 MMP 7 — fibroblast activation protein; MMP 7 — matipase; MMP 7 —
 stromelysin 3; MMP 7 — MMP 7; MMP 7 — MMP 9; MMP 7 — membrane
 type matrix metalloproteinase I; MMP 7 — a tumor antigen; MMP 9 — a
 cathepsin type protease; MMP 9 — cathepsin D; MMP 9 — to cathepsin K;
 MMP 9 — cathepsin L; MMP 9 — cathepsin O; MMP 9 — matipase; MMP 9 -
 20 — MMP 9; MMP 9 — membrane type matrix metalloproteinase I; MMP 9 — a
 tumor antigen; MMP 12 — a cathepsin type protease; MMP 12 — cathepsin D;
 MMP 12 — to cathepsin K; MMP 12 — cathepsin L; MMP 12 — cathepsin O;
 MMP 12 — matipase; MMP 12 — MMP 2; MMP 12 — membrane type matrix
 metalloproteinase I; MMP 12 — a tumor antigen; MMP 13 — a cathepsin type

protease; MMP 13 — cathepsin D; MMP 13 — to cathepsin K; MMP 13 — cathepsin L; MMP 13 — cathepsin O; MMP 13 — matipase; MMP 13 — membrane type matrix metalloproteinase I; MMP 13 — a tumor antigen; Membrane type matrix metalloproteinase — a cathepsin type protease;

- 5 Membrane type matrix metalloproteinase — cathepsin D; Membrane type matrix metalloproteinase — to cathepsin K; Membrane type matrix metalloproteinase — cathepsin L; Membrane type matrix metalloproteinase — cathepsin O; Membrane type matrix metalloproteinase — matipase; Membrane type matrix metalloproteinase — membrane type matrix metalloproteinase I; and Membrane
- 10 type matrix metalloproteinase — a tumor antigen.

56.) A compound of claim 55 that is also comprised of a third targeting ligand receptor that binds to a receptor that is present at increased amounts at a tumor cell compared to at a normal cell.

15

57.) A compound of claim 56 in which the third targeting ligand binds to PSMA or glutamate carboxypeptidase II.

- 58.) A compound of claim 55 in which the effector agent is comprised of a cytotoxic
- 20 drug.

59.) A compound of claim 55 in which the effector agent is comprised of a radionuclide.

60.) A compound of claim 55 in which the effector agent is comprised of a drug that stimulates the immune system.

61.) A compound of claim 55 in which the effector agent is comprised of a group that can irreversibly chemically modify one or more tumor components.

5

62.) A compound of claim 55 in which the effector agent comprises an inhibitor to multidrug transporter proteins.

63.) A compound of claim 55 in which the effector agent comprises an inhibitor to
10 nucleoside transporter proteins.

64.) A compound of claim 54 in which the effector agent is comprised of a group that can irreversibly chemically modify a biomolecule that is increased at a tumor cell compared to at a normal cell.

15

65.) A compound of claim 15 or claim 30 or claim 40 or claim 55 in which the effector agent comprises a cytotoxic drug selected from the following list:

- a. anthracyclines
- b. ellipticines
- 20 c. mitoxantrones
- d. Bleomycins
- e. taxols
- f. inhibitors of thymidylate synthase
- g. hydroxystaurosporine

- h. cryptophycin analogs
- i. vincristine
- j. vinblastine
- k. indanocene
- 5 l. mitomycin c
- m. phosphoramidate mustard analogs
- n. podophyllotoxins
- o. ecteinascidins
- p. didemnin
- 10 q. BW1843U89
- r. 2-pyrrolinodoxorubicin
- s. phthalascidin
- t. an inhibitor of glycylamide ribonucleotide transformylase
- u. an inhibitor hypoxanthine-guanine phosphoribosyltransferase
- 15 v. camptothecin
- w. trimetrexate
- x. a nucleoside transporter inhibitor
- y. mycophenolic acid
- z. an inhibitor of dihydroorotic acid dehydrogenase
- 20 aa. an inhibitor to Orotidine 5'-phosphate decarboxylase

66.) A compound of claim 15 in which the effector agent of ET is comprised of a group with the structure RN-L-V, wherein RN is a group that binds to the target biomolecule referred to as "m"; and L is a linker, and V is a group that can

covalently modify the target m; and wherein RN-L-V can bind to m and irreversibly chemically modify m.

67.) A compound of claim 66 in which V is comprised of a chemical group that
5 generates free radicals and wherein the generated free radicals irreversibly chemically modify the target biomolecule m.

68.) A compound of claim 67 in which the free radical generator V is a
10 nonradioactive metal- chelator complex.

69.) A compound of claim 23 in which the effector agent is comprised of a structure
that is modified by the enzymatic activity of a biomolecule and wherein this
modification inactivates said biomolecule and in the process irreversibly chemically
modifies said biomolecule.

15

70.) A compound of claim 10 further comprising a second group wherein said
second group binds to a receptor present in increased amounts at a target cell
compared to at a non-target cell and wherein said second group is comprised of:
a monoclonal antibody; or

20

- I. targeting receptor binding fragment of a monoclonal antibody; or
- II. an analog or derivative which bears amino acid sequence similarity to
portions of a monoclonal antibody; or
- III. a natural protein, or a complex of natural proteins, or a protein; or
- IV. a naturally occurring polymer.

71.) A compound comprised of a group, referred to as a "masked intracellular transport ligand" which can be modified in vivo to give a group referred to as an "intracellular transport ligand" which binds to a cell receptor that actively transports bound ligands into the cell.

5

72.) A compound of claim 71 wherein the masked intracellular transport ligand is comprised of masked folic acid.

10

73.) A compound of claim 71 wherein the masked intracellular transport ligand is comprised of masked biotin.

15

74.) A compound of claim 71 wherein the masked intracellular transport ligand is comprised of a group referred to as a trigger that is covalently bonded to an intracellular transport ligand, and wherein in vivo modification by enzymatic or spontaneous processes of said trigger referred to as "trigger activation" unmasks the intracellular transport ligand, and wherein there is a time delay between trigger activation and the chemical unmasking of the intracellular transport ligand, and wherein the time delay required for 50% unmasking of the intracellular transport ligand is in the range of about 30 minutes to about 4 hours.

20

75.) A method to deliver a targeted drug ET into a target cell, said method comprising the step of contacting the cell with the drug ET wherein ET is a compound of claim 71 further comprising a targeting ligand referred to as "T" that binds to the target cell, and an effector agent "E" with pharmacological activity.

25

76.) A method of claim 75 which is comprised of contacting cells with a compound of claim 71 and a second compound which is able to bind to the unmasked intracellular transport ligand and also bind, at the same time, to a cell surface receptor that transports bound ligands into the cells.

30

77.) A method of claim 76, wherein the masked intracellular transport ligand is comprised of masked biotin; and wherein the second compound is comprised of a biotin binding molecule coupled to a molecule that binds to a target receptor on the cell that transports bound ligands into the cell.

5

78.) A method of claim 77 wherein the second compound is comprised of a monoclonal antibody or fragment of a monoclonal antibody that is coupled to a biotin binding agent; and wherein the monoclonal antibody is selective for a target selective antigen on the surface of the target cell.

10

79.) A method of stimulating an immune response against a tumor and for treating a patient with cancer which comprises the following steps:

- I. Immunizing or sensitizing a patient to a compound referred to as a neoantigen; and
- 15 II. Administering to the patient a compound referred to as a neoantigen generating compound; wherein said compound can irreversibly chemically modify a component of the tumor resulting in the generation of said neoantigen at the tumor.

20 80.) A method of claim 79 in which the component of the tumor that is modified is enriched at a tumor cell compared to at a normal cell.

81.) A method of stimulating an immune response against a tumor and for treating a patient with cancer which comprises the following steps:

I. Immunizing or sensitizing a patient to a compound referred to as a neoantigen; and

5 II. Administering to the patient a compound of claim 22, referred to as a neoantigen generating compound; wherein said compound can irreversibly chemically modify a component of the tumor resulting in the generation of said neoantigen at the tumor.

10 82.) A method of claim 80 in which the tumor component modified is selected from the following list:

- 1) Prostate specific Antigen
- 2) Human glandular kallikrein 2
- 3) Prostatic acid phosphatase
- 15 4) Plasmin
- 5) Placental type alkaline phosphatase
- 6) Matriptase
- 7) Matrix metalloproteinases
- 8) Thymidine phosphorylase
- 20 9) Trypsin
- 10) Urokinase
- 11) Fatty Acid Synthase
- 12) Steroid sulfatase
- 13) Epidermal growth factor receptor
- 25 14) Mitogen activated protein kinase kinase
- 15) Phosphatidylinositol 3-kinase

- 16) Mitogen activated protein kinase
- 17) Mitogen activated protein kinase
- 18) Thymidylate synthase
- 19) Protein kinase A
- 5 20) Fibroblast activation protein/ seprase
- 21) P-glycoprotein

83.) A method of stimulating an immune response against a tumor and for treating a patient with cancer which comprises the following steps:

- 10 I. Immunizing or sensitizing a patient to a compound referred to as a neoantigen;
- II. Administering to the patient a compound of claim 22, referred to as a neoantigen generating compound; wherein said compound can irreversibly chemically modify a component of the tumor resulting in the generation of
- 15 said neoantigen at the tumor; and

wherein, the tumor component modified is selected from the following list:

- 1) Prostate specific Antigen
- 2) Human glandular kallikrein 2
- 3) Prostatic acid phosphatase
- 20 4) Plasmin
- 5) Placental type alkaline phosphatase
- 6) Matriptase
- 7) Matrix metalloproteinases
- 8) Thymidine phosphorylase
- 25 9) Trypsin
- 10) Urokinase
- 11) Fatty Acid Synthase

- 12) Steroid sulfatase
- 13) Epidermal growth factor receptor
- 14) Mitogen activated protein kinase kinase
- 15) Phosphatidylinositol 3-kinase
- 5 16) Mitogen activated protein kinase
- 17) Mitogen activated protein kinase
- 18) Thymidylate synthase
- 19) Protein kinase A
- 20) Fibroblast activation protein/ seprase
- 10 21) P-glycoprotein

84.) A set of anticancer drugs referred to as "E1T1" and "E2T2" for use together or for co-administration to a patient, wherein E1 and E2 are effector agents that
15 exhibit synergistic toxicity to a cell; and wherein T1 comprises a targeting ligand that binds to a first target receptor and T2 comprises a second targeting ligand that binds to the second target receptor which is increased on a tumor cell compared to a normal cell and where the first targeting ligand binds to a targeting receptor selected from the following list:

- 20 1) a cathepsin type protease
- 2) a collagenase
- 3) a gelatinase
- 4) a matrix metalloproteinase
- 5) a membrane type matrix metalloproteinase
- 25 6) alpha v beta 3 integrin
- 7) bombesin /gastrin releasing peptide receptors

- 8) cathepsin B
- 9) cathepsin D
- 10) cathepsin K
- 11) cathepsin L
- 5 12) cathepsin O
- 13) fibroblast activation protein
- 14) folate binding receptors
- 15) gastrin/cholecystokinin type B receptor
- 16) glutamate carboxypeptidase II or (PSMA)
- 10 17) guanidinobenzoatase
- 18) laminin receptor
- 19) matrilysin
- 20) matipase
- 21) melanocyte stimulating hormone receptor
- 15 22) nitrobenzylthioinosine-binding receptors
- 23) norepinephrine transporters
- 24) nucleoside transporter proteins
- 25) peripheral benzodiazepam binding receptors
- 26) plasmin
- 20 27) seprase
- 28) sigma receptors
- 29) somatostatin receptors
- 30) stromelysin 3
- 31) trypsin

- 32) urokinase
- 33) MMP 1
- 34) MMP 2
- 35) MMP 3
- 5 36) MMP 7
- 37) MMP 9
- 38) Membrane type matrix metalloproteinase I
- 39) MMP 12
- 40) MMP 13

10

85.) A set of compounds of claim 84 wherein the effector agent E1 inhibits the denovo synthesis of a biomolecule(s) that is necessary for cell replication and/or survival, and the effector agent E2 inhibits a salvage pathway(s) that can enable a cell to by- pass the metabolic block caused by E1.

15

86.) A set of compounds of E1T1 and E2T2 of claim 85 wherein T1 comprises a targeting ligand that binds to the first target receptor (a1); and T2 comprises a second targeting ligand that binds to the second target receptor (a2) indicated in the pairs of (a1 — a2) listed below:

20

- 1) urokinase — a cathepsin type protease;
- 2) urokinase — a collagenase;
- 3) urokinase — a gelatinase;
- 4) urokinase — a matrix metalloproteinase;
- 5) urokinase — a membrane type matrix metalloproteinase;

- 6) urokinase — alpha v beta 3 integrin;
- 7) urokinase — bombesin /gastrin releasing peptide receptors;
- 8) urokinase — cathepsin B;
- 9) urokinase — cathepsin D;
- 5 10) urokinase — to cathepsin K;
- 11) urokinase — cathepsin L;
- 12) urokinase — cathepsin O;
- 13) urokinase — fibroblast activation protein;
- 14) urokinase — folate binding receptors;
- 10 15) urokinase — gastrin/cholecystokinin type B receptor;
- 16) urokinase — glutamate carboxypeptidase II or (PSMA);
- 17) urokinase — guanidinobenzoatase;
- 18) urokinase — laminin receptor;
- 19) urokinase — matrilysin;
- 15 20) urokinase — matripase;
- 21) urokinase — melanocyte stimulating hormone receptor;
- 22) urokinase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 23) urokinase — norepinephrine transporters;
- 20 24) urokinase — nucleoside transporter proteins;
- 25) urokinase — peripheral benzodiazepam binding receptors;
- 26) urokinase — plasmin;
- 27) urokinase — seprase;
- 28) urokinase — sigma receptors;

- 29) urokinase — somatostatin receptors;
- 30) urokinase — stromelysin 3;
- 31) urokinase — trypsin;
- 32) urokinase — urokinase;
- 5 33) urokinase — MMP 1;
- 34) urokinase — MMP 2;
- 35) urokinase — MMP 3;
- 36) urokinase — MMP 7;
- 37) urokinase — MMP 9;
- 10 38) urokinase — membrane type matrix metalloproteinase I;
- 39) urokinase — MMP 12;
- 40) urokinase — MMP 13;
- 41) urokinase — a tumor antigen;
- 42) plasmin — a cathepsin type protease;
- 15 43) plasmin — a collagenase;
- 44) plasmin — a gelatinase;
- 45) plasmin — a matrix metalloproteinase;
- 46) plasmin — a membrane type matrix metalloproteinase;
- 47) plasmin — alpha v beta 3 integrin;
- 20 48) plasmin — bombesin /gastrin releasing peptide receptors;
- 49) plasmin — cathepsin B;
- 50) plasmin — cathepsin D;
- 51) plasmin — to cathepsin K;
- 52) plasmin — cathepsin L;

- 53) plasmin — cathepsin O;
- 54) plasmin — fibroblast activation protein;
- 55) plasmin — folate binding receptors;
- 56) plasmin — gastrin/cholecystokinin type B receptor;
- 5 57) plasmin — glutamate carboxypeptidase II or (PSMA);
- 58) plasmin — guanidinobenzoate;
- 59) plasmin — laminin receptor;
- 60) plasmin — matrilysin;
- 61) plasmin — matripase;
- 10 62) plasmin — melanocyte stimulating hormone receptor;
- 63) plasmin — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 64) plasmin — norepinephrine transporters;
- 65) plasmin — nucleoside transporter proteins;
- 15 66) plasmin — peripheral benzodiazepam binding receptors;
- 67) plasmin — plasmin;
- 68) plasmin — seprase;
- 69) plasmin — sigma receptors;
- 70) plasmin — somatostatin receptors;
- 20 71) plasmin — stromelysin 3;
- 72) plasmin — trypsin;
- 73) plasmin — urokinase;
- 74) plasmin — MMP 1;
- 75) plasmin — MMP 2;

- 76) plasmin — MMP 3;
- 77) plasmin — MMP 7;
- 78) plasmin — MMP 9;
- 79) plasmin — membrane type matrix metalloproteinase I ;
- 5 80) plasmin — MMP 12;
- 81) plasmin — MMP 13;
- 82) plasmin — a tumor antigen;
- 83) a collagenase — a cathepsin type protease;
- 84) a collagenase — a collagenase;
- 10 85) a collagenase — a gelatinase;
- 86) a collagenase — a matrix metalloproteinase;
- 87) a collagenase — a membrane type matrix metalloproteinase;
- 88) a collagenase — alpha v beta 3 integrin;
- 89) a collagenase — bombesin /gastrin releasing peptide receptors;
- 15 90) a collagenase — cathepsin B;
- 91) a collagenase — cathepsin D;
- 92) a collagenase — to cathepsin K;
- 93) a collagenase — cathepsin L;
- 94) a collagenase — cathepsin O;
- 20 95) a collagenase — fibroblast activation protein;
- 96) a collagenase — folate binding receptors;
- 97) a collagenase — gastrin/cholecystokinin type B receptor;
- 98) a collagenase — glutamate carboxypeptidase II or (PSMA);
- 99) a collagenase — guanidinobenzoatase;

- 100) a collagenase — laminin receptor;
- 101) a collagenase — matrilysin;
- 102) a collagenase — matripase;
- 103) a collagenase — melanocyte stimulating hormone receptor;
- 5 104) a collagenase — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
- 105) a collagenase — norepinephrine transporters;
- 106) a collagenase — nucleoside transporter proteins;
- 107) a collagenase — peripheral benzodiazepam binding receptors;
- 10 108) a collagenase — seprase;
- 109) a collagenase — sigma receptors;
- 110) a collagenase — somatostatin receptors;
- 111) a collagenase — stromelysin 3;
- 112) a collagenase — trypsin;
- 15 113) a collagenase — a collagenase;
- 114) a collagenase — MMP 1;
- 115) a collagenase — MMP 2;
- 116) a collagenase — MMP 3;
- 117) a collagenase — MMP 7;
- 20 118) a collagenase — MMP 9;
- 119) a collagenase — membrane type matrix metalloproteinase I;
- 120) a collagenase — MMP 12;
- 121) a collagenase — MMP 13;
- 122) a collagenase — a tumor antigen;

- 123) a gelatinase — a cathepsin type protease;
- 124) a gelatinase — a gelatinase;
- 125) a gelatinase — a matrix metalloproteinase;
- 126) a gelatinase — a membrane type matrix metalloproteinase;
- 5 127) a gelatinase — alpha v beta 3 integrin;
- 128) a gelatinase — bombesin /gastrin releasing peptide receptors;
- 129) a gelatinase — cathepsin B;
- 130) a gelatinase — cathepsin D;
- 131) a gelatinase — to cathepsin K;
- 10 132) a gelatinase — cathepsin L;
- 133) a gelatinase — cathepsin O;
- 134) a gelatinase — fibroblast activation protein;
- 135) a gelatinase — folate binding receptors;
- 136) a gelatinase — gastrin/cholecystokinin type B receptor;
- 15 137) a gelatinase — glutamate carboxypeptidase II or (PSMA);
- 138) a gelatinase — guanidinobenzoatase;
- 139) a gelatinase — laminin receptor;
- 140) a gelatinase — matrilysin;
- 141) a gelatinase — matripase;
- 20 142) a gelatinase — melanocyte stimulating hormone receptor;
- 143) a gelatinase — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
- 144) a gelatinase — norepinephrine transporters;
- 145) a gelatinase — nucleoside transporter proteins;

- 146) a gelatinase — peripheral benzodiazepam binding receptors;
- 147) a gelatinase — seprase;
- 148) a gelatinase — sigma receptors;
- 149) a gelatinase — somatostatin receptors;
- 5 150) a gelatinase — stromelysin 3;
- 151) a gelatinase — trypsin;
- 152) a gelatinase — MMP 1;
- 153) a gelatinase — MMP 2;
- 154) a gelatinase — MMP 3;
- 10 155) a gelatinase — MMP 7;
- 156) a gelatinase — MMP 9;
- 157) a gelatinase — membrane type matrix metalloproteinase I;
- 158) a gelatinase — MMP 12;
- 159) a gelatinase — MMP 13;
- 15 160) a gelatinase — a tumor antigen;
- 161) a matrix metalloproteinase — a cathepsin type protease;
- 162) a matrix metalloproteinase — a collagenase;
- 163) a matrix metalloproteinase — a gelatinase;
- 164) a matrix metalloproteinase — a matrix metalloproteinase;
- 20 165) a matrix metalloproteinase — a membrane type matrix
metalloproteinase;
- 166) a matrix metalloproteinase — alpha v beta 3 integrin;
- 167) a matrix metalloproteinase — bombesin /gastrin releasing peptide
receptors;

- 168) a matrix metalloproteinase — cathepsin B;
- 169) a matrix metalloproteinase — cathepsin D;
- 170) a matrix metalloproteinase — to cathepsin K;
- 171) a matrix metalloproteinase — cathepsin L;
- 5 172) a matrix metalloproteinase — cathepsin O;
- 173) a matrix metalloproteinase — fibroblast activation protein;
- 174) a matrix metalloproteinase — folate binding receptors;
- 175) a matrix metalloproteinase — gastrin/cholecystokinin type B receptor;
- 176) a matrix metalloproteinase — glutamate carboxypeptidase II or
10 (PSMA);
- 177) a matrix metalloproteinase — guanidinobenzoatase;
- 178) a matrix metalloproteinase — laminin receptor;
- 179) a matrix metalloproteinase — matrilysin;
- 180) a matrix metalloproteinase — matripase;
- 15 181) a matrix metalloproteinase — melanocyte stimulating hormone
receptor;
- 182) a matrix metalloproteinase — nitrobenzylthioinosine-binding receptors
or (nucleoside transporter);
- 183) a matrix metalloproteinase — norepinephrine transporters;
- 20 184) a matrix metalloproteinase — nucleoside transporter proteins;
- 185) a matrix metalloproteinase — peripheral benzodiazepam binding
receptors;
- 186) a matrix metalloproteinase — plasmin;
- 187) a matrix metalloproteinase — seprase;

- 188) a matrix metalloproteinase — sigma receptors;
- 189) a matrix metalloproteinase — somatostatin receptors;
- 190) a matrix metalloproteinase — stromelysin 3;
- 191) a matrix metalloproteinase — trypsin;
- 5 192) a matrix metalloproteinase — a matrix metalloproteinase;
- 193) a matrix metalloproteinase — MMP 1;
- 194) a matrix metalloproteinase — MMP 2;
- 195) a matrix metalloproteinase — MMP 3;
- 196) a matrix metalloproteinase — MMP 7;
- 10 197) a matrix metalloproteinase — MMP 9;
- 198) a matrix metalloproteinase — membrane type matrix
metalloproteinase I;
- 199) a matrix metalloproteinase — MMP 12;
- 200) a matrix metalloproteinase — MMP 13;
- 15 201) a matrix metalloproteinase — a tumor antigen;
- 202) a membrane type metalloproteinase — a cathepsin type protease;
- 203) a membrane type metalloproteinase — a membrane type matrix
metalloproteinase;
- 204) a membrane type metalloproteinase — alpha v beta 3 integrin;
- 20 205) a membrane type metalloproteinase — bombesin /gastrin releasing
peptide receptors;
- 206) a membrane type metalloproteinase — cathepsin B;
- 207) a membrane type metalloproteinase — cathepsin D;
- 208) a membrane type metalloproteinase — to cathepsin K;

- 209) a membrane type metalloproteinase — cathepsin L;
- 210) a membrane type metalloproteinase — cathepsin O;
- 211) a membrane type metalloproteinase — fibroblast activation protein;
- 212) a membrane type metalloproteinase — folate binding receptors;
- 5 213) a membrane type metalloproteinase — gastrin/cholecystokinin type B receptor;
- 214) a membrane type metalloproteinase — glutamate carboxypeptidase II or (PSMA);
- 215) a membrane type metalloproteinase — guanidinobenzoatase;
- 10 216) a membrane type metalloproteinase — laminin receptor;
- 217) a membrane type metalloproteinase — matrilysin;
- 218) a membrane type metalloproteinase — matripase;
- 219) a membrane type metalloproteinase — melanocyte stimulating hormone receptor;
- 15 220) a membrane type metalloproteinase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 221) a membrane type metalloproteinase — norepinephrine transporters;
- 222) a membrane type metalloproteinase — nucleoside transporter proteins;
- 20 223) a membrane type metalloproteinase — peripheral benzodiazepam binding receptors;
- 224) a membrane type metalloproteinase — seprase;
- 225) a membrane type metalloproteinase — sigma receptors;
- 226) a membrane type metalloproteinase — somatostatin receptors;

- 227) a membrane type metalloproteinase — stromelysin 3;
- 228) a membrane type metalloproteinase — trypsin;
- 229) a membrane type metalloproteinase — MMP 1;
- 230) a membrane type metalloproteinase — MMP 2;
- 5 231) a membrane type metalloproteinase — MMP 3;
- 232) a membrane type metalloproteinase — MMP 7;
- 233) a membrane type metalloproteinase — MMP 9;
- 234) a membrane type metalloproteinase — membrane type matrix metalloproteinase I;
- 10 235) a membrane type metalloproteinase — MMP 12;
- 236) a membrane type metalloproteinase — MMP 13;
- 237) a membrane type metalloproteinase — a tumor antigen;
- 238) alpha v beta 3 integrin — a cathepsin type protease;
- 239) alpha v beta 3 integrin — alpha v beta 3 integrin;
- 15 240) alpha v beta 3 integrin — bombesin /gastrin releasing peptide receptors;
- 241) alpha v beta 3 integrin — cathepsin B;
- 242) alpha v beta 3 integrin — cathepsin D;
- 243) alpha v beta 3 integrin — cathepsin K;
- 20 244) alpha v beta 3 integrin — cathepsin L;
- 245) alpha v beta 3 integrin — cathepsin O;
- 246) alpha v beta 3 integrin — fibroblast activation protein;
- 247) alpha v beta 3 integrin — folate binding receptors;
- 248) alpha v beta 3 integrin — gastrin/cholecystokinin type B receptor;

- 249) alpha v beta 3 integrin — glutamate carboxypeptidase II or (PSMA);
- 250) alpha v beta 3 integrin — guanidinobenzoatase;
- 251) alpha v beta 3 integrin — laminin receptor;
- 252) alpha v beta 3 integrin — matrilysin;
- 5 253) alpha v beta 3 integrin — matripase;
- 254) alpha v beta 3 integrin — melanocyte stimulating hormone receptor;
- 255) alpha v beta 3 integrin — nitrobenzylthioinosine-binding receptors; or
(nucleoside transporter);
- 256) alpha v beta 3 integrin — norepinephrine transporters;
- 10 257) alpha v beta 3 integrin — nucleoside transporter proteins;
- 258) alpha v beta 3 integrin — peripheral benzodiazepam binding
receptors;
- 259) alpha v beta 3 integrin — seprase;
- 260) alpha v beta 3 integrin — sigma receptors;
- 15 261) alpha v beta 3 integrin — somatostatin receptors;
- 262) alpha v beta 3 integrin — stromelysin 3;
- 263) alpha v beta 3 integrin — trypsin;
- 264) alpha v beta 3 integrin — MMP 1;
- 265) alpha v beta 3 integrin — MMP 2;
- 20 266) alpha v beta 3 integrin — MMP 3;
- 267) alpha v beta 3 integrin — MMP 7;
- 268) alpha v beta 3 integrin — MMP 9;
- 269) alpha v beta 3 integrin — membrane type matrix metalloproteinase I;
- 270) alpha v beta 3 integrin — MMP 12;

- 271) alpha v beta 3 integrin — MMP 13;
- 272) alpha v beta 3 integrin — a tumor antigen;
- 273) cathepsin B — a cathepsin type protease;
- 274) cathepsin B — bombesin /gastrin releasing peptide receptors;
- 5 275) cathepsin B — cathepsin B;
- 276) cathepsin B — cathepsin D;
- 277) cathepsin B — to cathepsin K;
- 278) cathepsin B — cathepsin L;
- 279) cathepsin B — cathepsin O;
- 10 280) cathepsin B — fibroblast activation protein;
- 281) cathepsin B — folate binding receptors;
- 282) cathepsin B — gastrin/cholecystokinin type B receptor;
- 283) cathepsin B — glutamate carboxypeptidase II or (PSMA);
- 284) cathepsin B — guanidinobenzoate;
- 15 285) cathepsin B — laminin receptor;
- 286) cathepsin B — matrilysin;
- 287) cathepsin B — matrilysin;
- 288) cathepsin B — melanocyte stimulating hormone receptor;
- 289) cathepsin B — nitrobenzylthioinosine-binding receptors or (nucleoside
20 transporter);
- 290) cathepsin B — norepinephrine transporters;
- 291) cathepsin B — nucleoside transporter proteins;
- 292) cathepsin B — peripheral benzodiazepam binding receptors;
- 293) cathepsin B — seprase;

- 294) cathepsin B — sigma receptors;
- 295) cathepsin B — somatostatin receptors;
- 296) cathepsin B — stromelysin 3;
- 297) cathepsin B — trypsin;
- 5 298) cathepsin B — MMP 1;
- 299) cathepsin B — MMP 2;
- 300) cathepsin B — MMP 3;
- 301) cathepsin B — MMP 7;
- 302) cathepsin B — MMP 9;
- 10 303) cathepsin B — membrane type matrix metalloproteinase I;
- 304) cathepsin B — MMP 12;
- 305) cathepsin B — MMP 13;
- 306) cathepsin B — a tumor antigen;
- 307) bombesin/ gastrin releasing peptide receptors — a cathepsin type
15 protease;
- 308) bombesin/ gastrin releasing peptide receptors — bombesin /gastrin
releasing peptide receptors;
- 309) bombesin/ gastrin releasing peptide receptors — cathepsin B;
- 310) bombesin/ gastrin releasing peptide receptors — cathepsin D;
- 20 311) bombesin/ gastrin releasing peptide receptors — to cathepsin K;
- 312) bombesin/ gastrin releasing peptide receptors — cathepsin L;
- 313) bombesin/ gastrin releasing peptide receptors — cathepsin O;
- 314) bombesin/ gastrin releasing peptide receptors — fibroblast activation
protein;

- 315) bombesin/ gastrin releasing peptide receptors — folate binding receptors;
- 316) bombesin/ gastrin releasing peptide receptors — gastrin/cholecystokinin type B receptor;
- 5 317) bombesin/ gastrin releasing peptide receptors — glutamate carboxypeptidase II or (PSMA);
- 318) bombesin/ gastrin releasing peptide receptors — guanidinobenzoatase;
- 319) bombesin/ gastrin releasing peptide receptors — laminin receptor;
- 10 320) bombesin/ gastrin releasing peptide receptors — matrilysin;
- 321) bombesin/ gastrin releasing peptide receptors — matripase;
- 322) bombesin/ gastrin releasing peptide receptors — melanocyte stimulating hormone receptor;
- 323) bombesin/ gastrin releasing peptide receptors — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 15 324) bombesin/ gastrin releasing peptide receptors — norepinephrine transporters;
- 325) bombesin/ gastrin releasing peptide receptors — nucleoside transporter proteins;
- 20 326) bombesin/ gastrin releasing peptide receptors — peripheral benzodiazepam binding receptors;
- 327) bombesin/ gastrin releasing peptide receptors — seprase;
- 328) bombesin/ gastrin releasing peptide receptors — sigma receptors;

- 329) bombesin/ gastrin releasing peptide receptors — somatostatin receptors;
- 330) bombesin/ gastrin releasing peptide receptors — stromelysin 3;
- 331) bombesin/ gastrin releasing peptide receptors — trypsin;
- 5 332) bombesin/ gastrin releasing peptide receptors — MMP 1;
- 333) bombesin/ gastrin releasing peptide receptors — MMP 2;
- 334) bombesin/ gastrin releasing peptide receptors — MMP 3;
- 335) bombesin/ gastrin releasing peptide receptors — MMP 7;
- 336) bombesin/ gastrin releasing peptide receptors — MMP 9;
- 10 337) bombesin/ gastrin releasing peptide receptors — membrane type matrix metalloproteinase I;
- 338) bombesin/ gastrin releasing peptide receptors — MMP 12;
- 339) bombesin/ gastrin releasing peptide receptors — MMP 13;
- 340) bombesin/ gastrin releasing peptide receptors — a tumor antigen;
- 15 341) fibroblast activation protein — a cathepsin type protease;
- 342) fibroblast activation protein — cathepsin D;
- 343) fibroblast activation protein — to cathepsin K;
- 344) fibroblast activation protein — cathepsin L;
- 345) fibroblast activation protein — cathepsin O;
- 20 346) fibroblast activation protein — fibroblast activation protein;
- 347) fibroblast activation protein — folate binding receptors;
- 348) fibroblast activation protein — gastrin/cholecystokinin type B receptor;
- 349) fibroblast activation protein — glutamate carboxypeptidase II or (PSMA);

- 350) fibroblast activation protein — guanidinobenzoate;
- 351) fibroblast activation protein — laminin receptor;
- 352) fibroblast activation protein — matrilysin;
- 353) fibroblast activation protein — matrilysin;
- 5 354) fibroblast activation protein — melanocyte stimulating hormone receptor;
- 355) fibroblast activation protein — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 356) fibroblast activation protein — norepinephrine transporters;
- 10 357) fibroblast activation protein — nucleoside transporter proteins;
- 358) fibroblast activation protein — peripheral benzodiazepam binding receptors;
- 359) fibroblast activation protein — plasmin;
- 360) fibroblast activation protein — seprase;
- 15 361) fibroblast activation protein — sigma receptors;
- 362) fibroblast activation protein — somatostatin receptors;
- 363) fibroblast activation protein — stromelysin 3;
- 364) fibroblast activation protein — trypsin;
- 365) fibroblast activation protein — MMP 1;
- 20 366) fibroblast activation protein — MMP 2;
- 367) fibroblast activation protein — MMP 3;
- 368) fibroblast activation protein — MMP 7;
- 369) fibroblast activation protein — MMP 9;

- 370) fibroblast activation protein — membrane type matrix metalloproteinase I ;
- 371) fibroblast activation protein — MMP 12;
- 372) fibroblast activation protein — MMP 13;
- 5 373) fibroblast activation protein — a tumor antigen;
- 374) glutamate carboxypeptidase II or PSMA — cathepsin D;
- 375) glutamate carboxypeptidase II or PSMA — to cathepsin K;
- 376) glutamate carboxypeptidase II or PSMA — cathepsin L;
- 377) glutamate carboxypeptidase II or PSMA — cathepsin O;
- 10 378) glutamate carboxypeptidase II or PSMA — fibroblast activation protein;
- 379) glutamate carboxypeptidase II or PSMA — folate binding receptors;
- 380) glutamate carboxypeptidase II or PSMA — gastrin/cholecystokinin type B receptor;
- 15 381) glutamate carboxypeptidase II or PSMA — glutamate carboxypeptidase II or (PSMA);
- 382) glutamate carboxypeptidase II or PSMA — guanidinobenzoatase;
- 383) glutamate carboxypeptidase II or PSMA — laminin receptor;
- 384) glutamate carboxypeptidase II or PSMA — matrilysin;
- 20 385) glutamate carboxypeptidase II or PSMA — matripase;
- 386) glutamate carboxypeptidase II or PSMA — melanocyte stimulating hormone receptor;
- 387) glutamate carboxypeptidase II or PSMA — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);

- 388) glutamate carboxypeptidase II or PSMA — nucleoside transporter proteins;
- 389) glutamate carboxypeptidase II or PSMA — peripheral benzodiazepam binding receptors;
- 5 390) glutamate carboxypeptidase II or PSMA — seprase;
- 391) glutamate carboxypeptidase II or PSMA — sigma receptors;
- 392) glutamate carboxypeptidase II or PSMA — somatostatin receptors;
- 393) glutamate carboxypeptidase II or PSMA — stromelysin 3;
- 394) glutamate carboxypeptidase II or PSMA — trypsin;
- 10 395) glutamate carboxypeptidase II or PSMA — MMP 1;
- 396) glutamate carboxypeptidase II or PSMA — MMP 2;
- 397) glutamate carboxypeptidase II or PSMA — MMP 3;
- 398) glutamate carboxypeptidase II or PSMA — MMP 7;
- 399) glutamate carboxypeptidase II or PSMA — MMP 9;
- 15 400) glutamate carboxypeptidase II or PSMA — membrane type matrix metalloproteinase I;
- 401) glutamate carboxypeptidase II or PSMA — MMP 12;
- 402) glutamate carboxypeptidase II or PSMA — MMP 13;
- 403) glutamate carboxypeptidase II or PSMA — a tumor antigen;
- 20 404) laminin receptor — a cathepsin type protease;
- 405) laminin receptor — cathepsin B;
- 406) laminin receptor — cathepsin D;
- 407) laminin receptor — to cathepsin K;
- 408) laminin receptor — cathepsin L;

- 409) laminin receptor — cathepsin O;
- 410) laminin receptor — fibroblast activation protein;
- 411) laminin receptor — folate binding receptors;
- 412) laminin receptor — gastrin/cholecystokinin type B receptor;
- 5 413) laminin receptor — guanidinobenzoatase;
- 414) laminin receptor — laminin receptor;
- 415) laminin receptor — matrilysin;
- 416) laminin receptor — matripase;
- 417) laminin receptor — melanocyte stimulating hormone receptor;
- 10 418) laminin receptor — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
- 419) laminin receptor — norepinephrine transporters;
- 420) laminin receptor — nucleoside transporter proteins;
- 421) laminin receptor — peripheral benzodiazepam binding receptors;
- 15 422) laminin receptor — seprase;
- 423) laminin receptor — sigma receptors;
- 424) laminin receptor — somatostatin receptors;
- 425) laminin receptor — stromelysin 3;
- 426) laminin receptor — trypsin;
- 20 427) laminin receptor — MMP 1;
- 428) laminin receptor — MMP 2;
- 429) laminin receptor — MMP 3;
- 430) laminin receptor — MMP 7;
- 431) laminin receptor — MMP 9;

- 432) laminin receptor — membrane type matrix metalloproteinase I;
433) laminin receptor — MMP 12;
434) laminin receptor — MMP 13;
435) laminin receptor — a tumor antigen;
5 436) seprase — a cathepsin type protease;
437) seprase — cathepsin D;
438) seprase — to cathepsin K;
439) seprase — cathepsin L;
440) seprase — cathepsin O;
10 441) seprase — fibroblast activation protein;
442) seprase — folate binding receptors;
443) seprase — gastrin/cholecystokinin type B receptor;
444) seprase — guanidinobenzoatase;
445) seprase — matripase;
15 446) seprase — melanocyte stimulating hormone receptor;
447) seprase — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
448) seprase — norepinephrine transporters;
449) seprase — nucleoside transporter proteins;
20 450) seprase — peripheral benzodiazepam binding receptors;
451) seprase — seprase;
452) seprase — sigma receptors;
453) seprase — somatostatin receptors;
454) seprase — stromelysin 3;

- 455) seprase — trypsin;
- 456) seprase — MMP 1;
- 457) seprase — MMP 2;
- 458) seprase — MMP 3;
- 5 459) seprase — MMP 7;
- 460) seprase — MMP 9;
- 461) seprase — membrane type matrix metalloproteinase I;
- 462) seprase — MMP 12;
- 463) seprase — MMP 13;
- 10 464) seprase — a tumor antigen;
- 465) guanidinobenzoatase — a cathepsin type protease;
- 466) guanidinobenzoatase — cathepsin D;
- 467) guanidinobenzoatase — to cathepsin K;
- 468) guanidinobenzoatase — cathepsin L;
- 15 469) guanidinobenzoatase — cathepsin O;
- 470) guanidinobenzoatase — fibroblast activation protein;
- 471) guanidinobenzoatase — folate binding receptors;
- 472) guanidinobenzoatase — gastrin/cholecystokinin type B receptor;
- 473) guanidinobenzoatase — guanidinobenzoatase;
- 20 474) guanidinobenzoatase — matripase;
- 475) guanidinobenzoatase — melanocyte stimulating hormone receptor;
- 476) guanidinobenzoatase — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
- 477) guanidinobenzoatase — norepinephrine transporters;

- 478) guanidinobenzoatase — nucleoside transporter proteins;
- 479) guanidinobenzoatase — peripheral benzodiazepam binding receptors;
- 480) guanidinobenzoatase — sigma receptors;
- 5 481) guanidinobenzoatase — somatostatin receptors;
- 482) guanidinobenzoatase — stromelysin 3;
- 483) guanidinobenzoatase — trypsin;
- 484) guanidinobenzoatase — MMP 1;
- 485) guanidinobenzoatase — MMP 2;
- 10 486) guanidinobenzoatase — MMP 3;
- 487) guanidinobenzoatase — MMP 7;
- 488) guanidinobenzoatase — MMP 9;
- 489) guanidinobenzoatase — membrane type matrix metalloproteinase I;
- 490) guanidinobenzoatase — MMP 12;
- 15 491) guanidinobenzoatase — MMP 13;
- 492) guanidinobenzoatase — a tumor antigen;
- 493) peripheral benzodiazepam binding receptors — a cathepsin type protease;
- 494) peripheral benzodiazepam binding receptors — cathepsin D;
- 20 495) peripheral benzodiazepam binding receptors — to cathepsin K;
- 496) peripheral benzodiazepam binding receptors — cathepsin L;
- 497) peripheral benzodiazepam binding receptors — cathepsin O;
- 498) peripheral benzodiazepam binding receptors — fibroblast activation protein;

- 499) peripheral benzodiazepam binding receptors — folate binding receptors;
- 500) peripheral benzodiazepam binding receptors — gastrin/cholecystokinin type B receptor;
- 5 501) peripheral benzodiazepam binding receptors — guanidinobenzoate;
- 502) peripheral benzodiazepam binding receptors — matrilysin;
- 503) peripheral benzodiazepam binding receptors — melanocyte stimulating hormone receptor;
- 10 504) peripheral benzodiazepam binding receptors — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 505) peripheral benzodiazepam binding receptors — norepinephrine transporters;
- 506) peripheral benzodiazepam binding receptors — nucleoside transporter proteins;
- 15 507) peripheral benzodiazepam binding receptors — peripheral benzodiazepam binding receptors;
- 508) peripheral benzodiazepam binding receptors — sigma receptors;
- 509) peripheral benzodiazepam binding receptors — somatostatin receptors;
- 20 510) peripheral benzodiazepam binding receptors — stromelysin 3;
- 511) peripheral benzodiazepam binding receptors — trypsin;
- 512) peripheral benzodiazepam binding receptors — MMP 1;
- 513) peripheral benzodiazepam binding receptors — MMP 2;

- 514) peripheral benzodiazepam binding receptors — MMP 3;
515) peripheral benzodiazepam binding receptors — MMP 7;
516) peripheral benzodiazepam binding receptors — MMP 9;
517) peripheral benzodiazepam binding receptors — membrane type
5 matrix metalloproteinase I;
518) peripheral benzodiazepam binding receptors — MMP 12;
519) peripheral benzodiazepam binding receptors — MMP 13;
520) peripheral benzodiazepam binding receptors — a tumor antigen;
521) folate binding receptors — a cathepsin type protease;
10 522) folate binding receptors — cathepsin D;
523) folate binding receptors — to cathepsin K;
524) folate binding receptors — cathepsin L;
525) folate binding receptors — cathepsin O;
526) folate binding receptors — fibroblast activation protein;
15 527) folate binding receptors — folate binding receptors;
528) folate binding receptors — matipase;
529) folate binding receptors — melanocyte stimulating hormone receptor;
530) folate binding receptors — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
20 531) folate binding receptors — norepinephrine transporters;
532) folate binding receptors — nucleoside transporter proteins;
533) folate binding receptors — sigma receptors;
534) folate binding receptors — somatostatin receptors;
535) folate binding receptors — stromelysin 3;

- 536) folate binding receptors — trypsin;
- 537) folate binding receptors — MMP 1;
- 538) folate binding receptors — MMP 2;
- 539) folate binding receptors — MMP 3;
- 5 540) folate binding receptors — MMP 7;
- 541) folate binding receptors — MMP 9;
- 542) folate binding receptors — membrane type matrix metalloproteinase 1;
- 543) folate binding receptors — MMP 12;
- 544) folate binding receptors — MMP 13;
- 10 545) folate binding receptors — a tumor antigen;
- 546) folate binding receptors — a cathepsin type protease;
- 547) folate binding receptors — cathepsin D;
- 548) folate binding receptors — to cathepsin K;
- 549) folate binding receptors — cathepsin L;
- 15 550) folate binding receptors — cathepsin O;
- 551) folate binding receptors — fibroblast activation protein;
- 552) folate binding receptors — folate binding receptors;
- 553) folate binding receptors — matipase;
- 554) folate binding receptors — melanocyte stimulating hormone receptor;
- 20 555) folate binding receptors — nitrobenzylthioinosine-binding receptors or
(nucleoside transporter);
- 556) folate binding receptors — norepinephrine transporters;
- 557) folate binding receptors — nucleoside transporter proteins;
- 558) folate binding receptors — sigma receptors;

- 559) folate binding receptors — somatostatin receptors;
- 560) folate binding receptors — stromelysin 3;
- 561) folate binding receptors — trypsin;
- 562) folate binding receptors — MMP 1;
- 5 563) folate binding receptors — MMP 2;
- 564) folate binding receptors — MMP 3;
- 565) folate binding receptors — MMP 7;
- 566) folate binding receptors — MMP 9;
- 567) folate binding receptors — membrane type matrix metalloproteinase I;
- 10 568) folate binding receptors — MMP 12;
- 569) folate binding receptors — MMP 13;
- 570) folate binding receptors — a tumor antigen;
- 571) nucleoside transporter proteins — a cathepsin type protease;
- 572) nucleoside transporter proteins — cathepsin D;
- 15 573) nucleoside transporter proteins — to cathepsin K;
- 574) nucleoside transporter proteins — cathepsin L;
- 575) nucleoside transporter proteins — cathepsin O;
- 576) nucleoside transporter proteins — fibroblast activation protein;
- 577) nucleoside transporter proteins — nucleoside transporter proteins;
- 20 578) nucleoside transporter proteins — matipase;
- 579) nucleoside transporter proteins — melanocyte stimulating hormone
receptor;
- 580) nucleoside transporter proteins — nitrobenzylthioinosine-binding
receptors or (nucleoside transporter);

- 581) nucleoside transporter proteins — norepinephrine transporters;
- 582) nucleoside transporter proteins — nucleoside transporter proteins;
- 583) nucleoside transporter proteins — sigma receptors;
- 584) nucleoside transporter proteins — somatostatin receptors;
- 5 585) nucleoside transporter proteins — stromelysin 3;
- 586) nucleoside transporter proteins — trypsin;
- 587) nucleoside transporter proteins — MMP 1;
- 588) nucleoside transporter proteins — MMP 2;
- 589) nucleoside transporter proteins — MMP 3;
- 10 590) nucleoside transporter proteins — MMP 7;
- 591) nucleoside transporter proteins — MMP 9;
- 592) nucleoside transporter proteins — membrane type matrix metalloproteinase I;
- 593) nucleoside transporter proteins — MMP 12;
- 15 594) nucleoside transporter proteins — MMP 13;
- 595) nucleoside transporter proteins — a tumor antigen;
- 596) melanocyte stimulating hormone receptor — a cathepsin type protease;
- 597) melanocyte stimulating hormone receptor — cathepsin D;
- 20 598) melanocyte stimulating hormone receptor — to cathepsin K;
- 599) melanocyte stimulating hormone receptor — cathepsin L;
- 600) melanocyte stimulating hormone receptor — cathepsin O;
- 601) melanocyte stimulating hormone receptor — fibroblast activation protein;

- 602) melanocyte stimulating hormone receptor — melanocyte stimulating hormone receptor;
- 603) melanocyte stimulating hormone receptor — melanocyte stimulating hormone receptor;
- 5 604) melanocyte stimulating hormone receptor — nitrobenzylthioinosine-binding receptors or (nucleoside transporter);
- 605) melanocyte stimulating hormone receptor — norepinephrine transporters;
- 10 606) melanocyte stimulating hormone receptor — nucleoside transporter proteins;
- 607) melanocyte stimulating hormone receptor — sigma receptors;
- 608) melanocyte stimulating hormone receptor — somatostatin receptors;
- 609) melanocyte stimulating hormone receptor — stromelysin 3;
- 610) melanocyte stimulating hormone receptor — trypsin;
- 15 611) melanocyte stimulating hormone receptor — MMP 1;
- 612) melanocyte stimulating hormone receptor — MMP 2;
- 613) melanocyte stimulating hormone receptor — MMP 3;
- 614) melanocyte stimulating hormone receptor — MMP 7;
- 615) melanocyte stimulating hormone receptor — MMP 9;
- 20 616) melanocyte stimulating hormone receptor — membrane type matrix metalloproteinase I;
- 617) melanocyte stimulating hormone receptor — MMP 12;
- 618) melanocyte stimulating hormone receptor — MMP 13;
- 619) melanocyte stimulating hormone receptor — a tumor antigen;

- 620) sigma receptors — a cathepsin type protease;
- 621) sigma receptors — cathepsin D;
- 622) sigma receptors — to cathepsin K;
- 623) sigma receptors — cathepsin L;
- 5 624) sigma receptors — cathepsin O;
- 625) sigma receptors — fibroblast activation protein;
- 626) sigma receptors — sigma receptors;
- 627) sigma receptors — matipase;
- 628) sigma receptors — norepinephrine transporters;
- 10 629) sigma receptors — sigma receptors;
- 630) sigma receptors — somatostatin receptors;
- 631) sigma receptors — stromelysin 3;
- 632) sigma receptors — trypsin;
- 633) sigma receptors — MMP 1;
- 15 634) sigma receptors — MMP 2;
- 635) sigma receptors — MMP 3;
- 636) sigma receptors — MMP 7;
- 637) sigma receptors — MMP 9;
- 638) sigma receptors — membrane type matrix metalloproteinase I;
- 20 639) sigma receptors — MMP 12;
- 640) sigma receptors — MMP 13;
- 641) sigma receptors — a tumor antigen;
- 642) somatostatin receptors — a cathepsin type protease;
- 643) somatostatin receptors — cathepsin D;

- 644) somatostatin receptors — to cathepsin K;
- 645) somatostatin receptors — cathepsin L;
- 646) somatostatin receptors — cathepsin O;
- 647) somatostatin receptors — fibroblast activation protein;
- 5 648) somatostatin receptors — somatostatin receptors;
- 649) somatostatin receptors — matrilysin;
- 650) somatostatin receptors — melanocyte stimulating hormone receptor;
- 651) somatostatin receptors — sigma receptors;
- 652) somatostatin receptors — somatostatin receptors;
- 10 653) somatostatin receptors — stromelysin 3;
- 654) somatostatin receptors — trypsin;
- 655) somatostatin receptors — MMP 1;
- 656) somatostatin receptors — MMP 2;
- 657) somatostatin receptors — MMP 3;
- 15 658) somatostatin receptors — MMP 7;
- 659) somatostatin receptors — MMP 9;
- 660) somatostatin receptors — membrane type matrix metalloproteinase I;
- 661) somatostatin receptors — MMP 12;
- 662) somatostatin receptors — MMP 13;
- 20 663) somatostatin receptors — a tumor antigen ;
- 664) stromelysin 3 — a cathepsin type protease;
- 665) stromelysin 3 — cathepsin D;
- 666) stromelysin 3 — to cathepsin K;
- 667) stromelysin 3 — cathepsin L;

- 668) stromelysin 3 — cathepsin O;
- 669) stromelysin 3 — fibroblast activation protein;
- 670) stromelysin 3 — stromelysin 3;
- 671) stromelysin 3 — matipase;
- 5 672) stromelysin 3 — melanocyte stimulating hormone receptor;
- 673) stromelysin 3 — somatostatin receptors;
- 674) stromelysin 3 — trypsin;
- 675) stromelysin 3 — MMP 1;
- 676) stromelysin 3 — MMP 2;
- 10 677) stromelysin 3 — MMP 3;
- 678) stromelysin 3 — MMP 7;
- 679) stromelysin 3 — MMP 9;
- 680) stromelysin 3 — membrane type matrix metalloproteinase I;
- 681) stromelysin 3 — MMP 12;
- 15 682) stromelysin 3 — MMP 13;
- 683) stromelysin 3 — a tumor antigen;
- 684) trypsin — a cathepsin type protease;
- 685) trypsin — cathepsin D;
- 686) trypsin — to cathepsin K;
- 20 687) trypsin — cathepsin L;
- 688) trypsin — cathepsin O;
- 689) trypsin — fibroblast activation protein;
- 690) trypsin — trypsin;
- 691) trypsin — matipase;

- 692) trypsin — melanocyte stimulating hormone receptor;
693) trypsin — stromelysin 3;
694) trypsin — MMP 1;
695) trypsin — MMP 2;
5 696) trypsin — MMP 3;
697) trypsin — MMP 7;
698) trypsin — MMP 9;
699) trypsin — membrane type matrix metalloproteinase I;
700) trypsin — MMP 12;
10 701) trypsin — MMP 13;
702) trypsin — a tumor antigen;
703) MMP 1 — a cathepsin type protease;
704) MMP 1 — cathepsin D;
705) MMP 1 — to cathepsin K;
15 706) MMP 1 — cathepsin L;
707) MMP 1 — cathepsin O;
708) MMP 1 — fibroblast activation protein;
709) MMP 1 — matipase;
710) MMP 1 — melanocyte stimulating hormone receptor;
20 711) MMP 1 — stromelysin 3;
712) MMP 1 — MMP 1;
713) MMP 1 — MMP 2;
714) MMP 1 — MMP 3;
715) MMP 1 — MMP 7;

- 716) MMP 1 — MMP 9;
- 717) MMP 1 — membrane type matrix metalloproteinase I;
- 718) MMP 1 — MMP 12;
- 719) MMP 1 — MMP 13;
- 5 720) MMP 1 — a tumor antigen;
- 721) MMP-2 — a cathepsin type protease;
- 722) MMP-2 — cathepsin D;
- 723) MMP-2 — to cathepsin K;
- 724) MMP-2 — cathepsin L;
- 10 725) MMP-2 — cathepsin O;
- 726) MMP-2 — fibroblast activation protein;
- 727) MMP-2 — matipase;
- 728) MMP-2 — melanocyte stimulating hormone receptor;
- 729) MMP-2 — stromelysin 3;
- 15 730) MMP-2 — MMP 2;
- 731) MMP-2 — MMP 3;
- 732) MMP-2 — MMP 7;
- 733) MMP-2 — MMP 9;
- 734) MMP-2 — membrane type matrix metalloproteinase I;
- 20 735) MMP-2 — MMP-2;
- 736) MMP-2 — MMP-3;
- 737) MMP-2 — a tumor antigen;
- 738) MMP-3 — a cathepsin type protease;
- 739) MMP-3 — cathepsin D;

- 740) MMP-3 — to cathepsin K;
741) MMP-3 — cathepsin L;
742) MMP-3 — cathepsin O;
743) MMP-3 — matrilysin;
5 744) MMP-3 — MMP 3;
745) MMP-3 — MMP 7;
746) MMP-3 — MMP 9;
747) MMP-3 — membrane type matrix metalloproteinase 1;
748) MMP-3 — MMP-3;
10 749) MMP-3 — a tumor antigen;
750) MMP 7 — a cathepsin type protease;
751) MMP 7 — cathepsin D;
752) MMP 7 — to cathepsin K;
753) MMP 7 — cathepsin L;
15 754) MMP 7 — cathepsin O;
755) MMP 7 — fibroblast activation protein;
756) MMP 7 — matrilysin;
757) MMP 7 — stromelysin 3;
758) MMP 7 — MMP 7;
20 759) MMP 7 — MMP 9;
760) MMP 7 — membrane type matrix metalloproteinase 1;
761) MMP 7 — a tumor antigen;
762) MMP 9 — a cathepsin type protease;
763) MMP 9 — cathepsin D;

- 764) MMP 9 — to cathepsin K;
- 765) MMP 9 — cathepsin L;
- 766) MMP 9 — cathepsin O;
- 767) MMP 9 — matipase;
- 5 768) MMP 9 — MMP 9;
- 769) MMP 9 — membrane type matrix metalloproteinase I;
- 770) MMP 9 — a tumor antigen;
- 771) MMP 12 — a cathepsin type protease;
- 772) MMP 12 — cathepsin D;
- 10 773) MMP 12 — to cathepsin K;
- 774) MMP 12 — cathepsin L;
- 775) MMP 12 — cathepsin O;
- 776) MMP 12 — matipase;
- 777) MMP 12 — MMP 2;
- 15 778) MMP 12 — membrane type matrix metalloproteinase I;
- 779) MMP 12 — a tumor antigen;
- 780) MMP 13 — a cathepsin type protease;
- 781) MMP 13 — cathepsin D;
- 782) MMP 13 — to cathepsin K;
- 20 783) MMP 13 — cathepsin L;
- 784) MMP 13 — cathepsin O;
- 785) MMP 13 — matipase;
- 786) MMP 13 — membrane type matrix metalloproteinase I;
- 787) MMP 13 — a tumor antigen;

- 788) Membrane type matrix metalloproteinase --- a cathepsin type protease;
- 789) Membrane type matrix metalloproteinase --- cathepsin D;
- 790) Membrane type matrix metalloproteinase --- to cathepsin K;
- 5 791) Membrane type matrix metalloproteinase --- cathepsin L;
- 792) Membrane type matrix metalloproteinase --- cathepsin O;
- 793) Membrane type matrix metalloproteinase --- matrilysin;
- 794) Membrane type matrix metalloproteinase --- membrane type matrix metalloproteinase I; and
- 10 795) Membrane type matrix metalloproteinase --- a tumor antigen.

87.) A cancer diagnostic drug ET comprised of an effector group E that is comprised of one or more effector agents that enable tumor imaging and wherein T
15 is comprised of:

- a) A group referred to as a "tumor selective targeting ligand" which selectively binds to a target receptor that is increased on the surface of the tumor cell or in the microenvironment of the tumor cell compared to that for vital normal cells; and
- 20 b) One or more of the following groups:
 - I. A tumor selective targeting ligand;
 - II. A group, referred to as a "masked intracellular transport ligand" which can be modified in vivo to give a group referred to as an "intracellular

transport ligand" which binds to a tumor cell receptor that actively transports bound ligands into the tumor cell;

III. A group referred to as a "trigger" that can be modified in vivo, wherein in vivo modification activates the trigger and increases the imaging
5 signal at tumor cells or decreases the imaging signal intensity at nontumor cells; and

IV. A group referred to as an "intracellular trapping ligand", which binds to one or more intracellular receptors or a group referred to as a "masked
intracellular trapping ligand" which can be modified in vivo to give an
10 "intracellular trapping ligand".

and wherein when T is comprised of a second targeting ligand the first and second targeting ligands are able to bind simultaneously to two targeting receptor
molecules;

15

and provided that T is not: an antibody, or an analog or component of an antibody, or a complex of antibodies, or a bispecific antibody, or an analog of a bispecific antibody, or a natural protein, or a complex of natural proteins, or a protein, or a naturally occurring polymer, or a radiolabelled dimer, or a polymer to which is

20

attached at multiple sites one or more diagnostic imaging drugs.

88.) A compound of claim 87 in which the diagnostic imaging agent is comprised of a radionuclide.